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Title:
CARBOXYAMIDO DERIVATIVES

Abstract:

A carboxyamido derivative represented by formula (I) useful as a medicament for preventive and/or therapeutic treatment of a disease caused by tau protein kinase 1 hyperactivity: wherein R<1> represents 2-hydroxybenzimidazolyl group which may be substituted and the like; Y represents oxygen atom or sulfur atom; R<2> represents hydrogen atom or an alkyl group; n represents 0, 1 or 2; at least one of X<1>, X<2>, X<3, X?4> and X<5> represent (a) NR<3> R<4>, (b) N+R<5>R<6>R<7>, or (c) a nitrogen-containing heterocyclic group having one or more sp<2> nitrogen atoms which may be substituted, in which R<3> and R<4> independently represent hydrogen atom, an alkyl group and the like, or R<3>, N and R<4> may combine together to form a nitrogen-containing heterocyclic group which may be substituted; R<5>, R<6> and R<7> represent an alkyl group and the like, or R<5>, N and R<6> may combine together to form a nitrogen-containing heterocyclic group which may be substituted; or neighboring X<2> and X<3> or X<3> and X<4> and the like may combine together with the benzene ring to form an isoindoline ring and the like, and the rest of them represent hydrogen atom.

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WO 01/42224 A1

(54) Title: CARBOXYAMIDO DERIVATIVES

(57) Abstract: A carboxyamido derivative represented by formula (I) useful as a medicament for preventive and/or therapeutic treatment of a disease caused by tau protein kinase 1 hyperactivity: wherein R^1 represents 2-hydroxybenzimidazolyl group which may be substituted and the like; Y represents oxygen atom or sulfur atom; R^2 represents hydrogen atom or an alkyl group; n represents 0, 1 or 2; at least one of X^1, X^2, X?3, X^4 and X^5 represent (a) NR^3R^4, (b) $N+R^5R^6R^7$, or (c) a nitrogen-containing heterocyclic group having one or more sp^2 nitrogen atoms which may be substituted, in which R^3 and R^4 independently represent hydrogen atom, an alkyl group and the like, or R^3, N and R^4 may combine together to form a nitrogen-containing heterocyclic group which may be substituted; R^5, R^6 and R^7 represent an alkyl group and the like, or R^5, N and R^6 may combine together to form a nitrogen-containing heterocyclic group which may be substituted; or neighboring X^2 and X^3 or X^3 and X^4 and the like may combine together with the benzene ring to form an isoindoline ring and the like, and the rest of them represent hydrogen atom.

DESCRIPTION

CARBOXYAMIDO DERIVATIVES

Technical Field

The present invention relates to novel carboxyamido derivatives that are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of diseases caused by tau protein kinase 1 hyperactivity, such as Alzheimer disease and the like.

Background Art

Alzheimer disease is progressive senile dementia, in which marked cerebral cortical atrophy is observed due to degeneration of nerve cells and decrease of nerve cell number. Pathologically, numerous senile plaques and neurofibrillary tangles are observed in brain. The number of patients has increased with the increment of aged population, and the disease arises a serious social problem. Although various theories have been proposed, a cause of the disease has not yet been elucidated. Early resolution of the cause has been desired.

It has been known that the degree of appearance of two characteristic pathological changes of Alzheimer disease well correlates to the degree of intellectual dysfunction. Therefore, researches have been conducted from early 1980's to reveal the cause of the disease through molecular level investigations of components of the two pathological changes. Senile plaques accumulate extracellularly, and amyloid β protein has been elucidated as their main component (abbreviated as "Aβ" hereinafter in the specification: Biochem. Biophys. Res. Commun., 120, 855 (1984); EMBO J., 4, 2757 (1985); Proc. Natl. Acad. Sci. USA, 82, 4245 (1985)). In the other pathological change, i.e., the neurofibrillary tangles, a double-helical filamentous

substance called paired helical filament (abbreviated as "PHF" hereinafter in the specification) accumulate intracellularly, and tau protein, which is a kind of microtubule-associated protein specific for brain, has been revealed as its main component (Proc. Natl. Acad. Sci. USA, 85, 4506 (1988); Neuron, 1, 827 (1988)).

Furthermore, on the basis of genetic investigations, presenilins 1 and 2 were found as causative genes of familial Alzheimer disease (Nature, 375, 754 (1995); Science, 269, 973 (1995); Nature. 376, 775 (1995)), and it has been revealed that presence of mutants of presenilins 1 and 2 promotes the secretion of Aβ (Neuron, 17, 1005 (1996); Proc. Natl. Acad. Sci. USA, 94, 2025 (1997)). From these results, it is considered that, in Alzheimer disease, Aβ abnormally accumulates and agglomerates due to a certain reason, which engages with the formation of PHF to cause death of nerve cells. It is also expected that extracellular outflow of glutamic acid and activation of glutamate receptor responding to the outflow may possibly be important factors in an early process of the nerve cell death caused by ischemic cerebrovascular accidents (Sai-shin Igaku [Latest Medicine], 49, 1506 (1994)).

It has been reported that kainic acid treatment that stimulates the AMPA receptor, one of glutamate receptor, increases mRNA of the amyloid precursor protein (abbreviated as "APP" hereinafter in the specification) as a precursor of Aβ (Society for Neuroscience Abstracts, 17, 1445 (1991)), and also promotes metabolism of APP (The Journal of Neuroscience, 10, 2400 (1990)). Therefore, it has been strongly suggested that the accumulation of Aβ is involved in cellular death due to ischemic cerebrovascular disorders. Other diseases in which abnormal accumulation and agglomeration of Aβ are observed include, for example, Down syndrome, cerebral bleeding due to solitary cerebral amyloid angiopathy, Lewy body disease (Shin-kei Shinpo [Nerve Advance], 34, 343 (1990); Tanpaku-shitu Kaku-san Koso [Protein, Nucleic Acid, Enzyme], 41, 1476 (1996)) and the like. Furthermore, as diseases showing neurofibrillary tangles due to the PHF accumulation, examples include

progressive supranuclear palsy, subacute sclerosing panencephalitis, postencephalitic parkinsonism, pugilistic encephalosis, Guam parkinsonism-dementia complex, Lewy body disease and the like (Tanpakushitu Kakusan Koso [Protein, Nucleic Acid, Enzyme], 36, 2 (1991); Igaku no Ayumi [Progress of Medicine], 158, 511 (1991); Tanpakushitu Kakusan Koso [Protein, Nucleic Acid, Enzyme], 41, 1476 (1996)).

The tau protein is generally composed of a group of related proteins that forms several bands at molecular weights of 48-65 kDa in SDS-polyacrylamide gel electrophoresis, and it promotes the formation of microtubules. It has been verified that tau protein incorporated in the PHF in the brain suffering from Alzheimer disease is abnormally phosphorylated compared with usual tau protein (J. Biochem., 99, 1807 (1986); Proc. Natl. Acad. Sci. USA, 83, 4913 (1986)). An enzyme catalyzing the abnormal phosphorylation has been isolated. The protein was named as tau protein kinase 1 (abbreviated as "TPK1" hereinafter in the specification), and its physicochemical properties have been elucidated (Seikagaku [Biochemistry], 64, 308 (1992); J. Biol. Chem., 267, 10897 (1992)). Moreover, cDNA of rat TPK1 was cloned from a rat cerebral cortex cDNA library based on a partial amino acid sequence of TPK1, and its nucleotide sequence was determined and an amino acid sequence was deduced (Japanese Patent Un-examined Publication [Kokai] No. 6-239893/1994). As a result, it has been revealed that the primary structure of the rat TPK1 corresponds to that of the enzyme known as rat GSK-3 β (glycogen synthase kinase 3 β, FEBS Lett., 325, 167 (1993)).

It has been reported that Aβ, the main component of senile plaques, is neurotoxic (Science, 250, 279 (1990)). However, various theories have been proposed as for the reason why Aβ causes the cell death, and any authentic theory has not yet been established. Takashima et al. observed that the cell death was caused by Aβ treatment of fetal rat hippocampus primary culture system, and then found that the TPK1 activity was increased by Aβ treatment and the cell death by Aβ was

inhibited by antisense of TPK1 (Proc. Natl. Acad. Sci. USA, 90, 7789 (1993); Japanese Patent Un-examined Publication [Kokai] No. 6-329551/1994).

In view of the foregoing, compounds which inhibit the TPK1 activity may possibly suppress the neurotoxicity of Aβ and the formation of PHF and inhibit the nerve cell death in the Alzheimer disease, thereby cease or defer the progress of the disease. The compounds may also be possibly used as a medicament for therapeutic treatment of ischemic cerebrovascular disorder, Down syndrome, solitary cerebral amyloid angiopathy, cerebral bleeding due to Lewy body disease and the like by suppressing the cytotoxicity of Aβ. Furthermore, the compounds may possibly be used as a medicament for therapeutic treatment of neurodegenerative diseases such as progressive supranuclear palsy, subacute sclerosing panencephalitis, postencephalitic parkinsonism, pugilistic encephalosis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration and frontotemporal dementia.

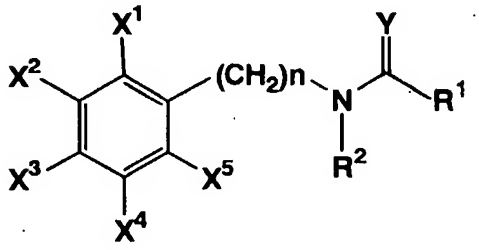
Disclosure of the Invention

An object of the present invention is to provide compounds useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of diseases such as Alzheimer disease and the like. More specifically, the object is to provide novel compounds useful as an active ingredient of a medicament that enables radical prevention and/or treatment of the diseases such as Alzheimer disease by inhibiting the TPK1 activity to suppress the neurotoxicity of Aβ and the formation of the PHF and by inhibiting the drop of nerve cells. Another object of the present invention is to provide the medicament having the aforementioned features.

In order to achieve the foregoing object, the inventors of the present invention conducted screenings of various compounds having inhibitory activity against the phosphorylation of TPK1. As a result, they found that compounds

represented by the following formula (I) had the desired activity and were useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of the aforementioned diseases. The present invention was achieved on the basis of these findings.

The present invention thus provides carboxyamido derivatives represented by formula (I) or salts thereof, or solvates thereof or hydrates thereof:



(I)

wherein R^1 represents 2-hydroxybenzimidazolyl group which may be substituted or 2-hydroxynaphthoimidazolyl group which may be substituted;

Y represents oxygen atom or sulfur atom;

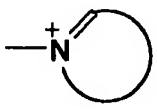
R^2 represents hydrogen atom or an alkyl group having from 1 to 5 carbon atoms;

n represents 0, 1 or 2;

X^1, X^2, X^3, X^4 and X^5 represent

(1) at least one of them represents a group represented by –P-A-Q-Z

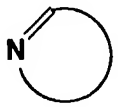
in which symbol "P" and "Q" independently represent a bond or an alkylene group having from 1 to 5 carbon atoms, symbol "A" represents a bond, oxygen atom, sulfur atom, -SO- or $-SO_2-$, symbol "Z" represents (a) NR^3R^4, (b) $N^+R^5R^6R^7$, or a group represented by formula (c):



(c)

in which R^3 and R^4 independently represent hydrogen atom, an alkyl group having from 1 to 15 carbon atoms which may be substituted, an aryl group having from 6 to 12 carbon atoms which may be substituted, a heterocyclic group which may be substituted, R^8-CO-, R^8-O-CO- or R^8-SO_2- (R^8 represents an alkyl group having from 1 to 15 carbon atoms which may be substituted, an aryl group having from 6 to 12 carbon atoms which may be substituted, or a heterocyclic group which may be substituted), or R^3, N and R^4 may combine together to form a nitrogen-containing heterocyclic group which may be substituted; R^5, R^6 and R^7 independently represent an alkyl group having from 1 to 15 carbon atoms which may be substituted, an aryl group having from 6 to 12 carbon atoms which may be substituted, a heterocyclic group which may be substituted, or R^5, N and R^6 may combine together to form a nitrogen-containing heterocyclic group which may be substituted; and

the group of the formula:



represents a nitrogen-containing heterocyclic group having one or more sp^2 nitrogen atoms which may be substituted; or

(2) neighboring X^1 and X^2, X^2 and X^3, X^3 and X^4, or X^4 and X^5 may combine together with the benzene ring to form an isoindoline ring which may be substituted or a tetrahydroisoquinoline ring which may be substituted; and

(3) the rest of X^1, X^2, X^3, X^4 and X^5 independently represent hydrogen atom, an alkyl group having from 1 to 5 carbon atoms, or an alkoxyl group having from 1 to 5 carbon atoms.

According to another aspect of the present invention, there is provided a medicament for preventive and/or therapeutic treatment of a disease caused by tau

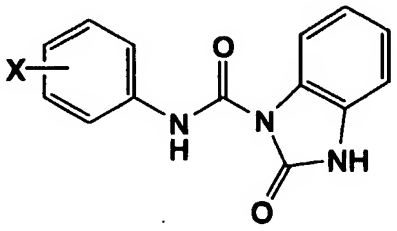
protein kinase 1 hyperactivity or a neurodegenerative disease which comprises as an active ingredient a substance selected from the group consisting of a compound represented by formula (I) and a salt thereof, and a solvate thereof and a hydrate thereof.

According to a preferred embodiment of the present invention, there is provided the aforementioned medicament wherein the diseases are selected from the group consisting of Alzheimer disease, ischemic cerebrovascular accidents, Down syndrome, cerebral bleeding due to cerebral amyloid angiopathy, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration and frontotemporal dementia. Also as a preferred embodiment, the aforementioned medicament in the form of pharmaceutical composition containing the above substance as an active ingredient together with one or more pharmaceutical additives is provided. The present invention further provides an inhibitor of tau protein kinase 1 comprising as an active ingredient a substance selected from the group consisting of the carboxyamido derivatives of formula (I) and the salts thereof, and the solvates thereof and the hydrates thereof.

According to further aspects of the present invention, there are provided a method for preventive and/or therapeutic treatment of diseases caused by tau protein kinase 1 hyperactivity, which comprises the step of administering to a patient a preventively and/or therapeutically effective amount of a substance selected from the group consisting of the carboxyamido derivatives of formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof; and a use of a substance selected from the group consisting of the carboxyamido derivatives of formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof for the manufacture of the

aforementioned medicament.

As for compounds structurally similar to the carboxyamido derivatives represented by the aforementioned formula (I), compounds represented by the following formula (II) are known (Japanese Patent Un-examined Publication [Kokai] No. 149277/1982):

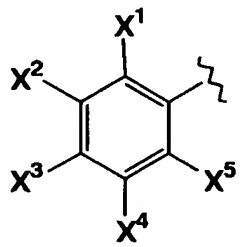


(II)

wherein X represents o-chloro, m-chloro, p-chloro, p-methoxy group, p-methyl group, m-trifluoromethyl group. However, X of the compounds disclosed in the above patent document is small bulk and a simple functional group such as chlorine atom, methoxy group, methyl group and trifluoromethyl group. Accordingly, the prior known compounds are structurally much different from the compound of the present invention. Moreover, the patent document discloses that pharmacological activity of these compounds is antiedemic effect and analgesic effect, which is distinguishable from the pharmacological activity of the compound of the present invention.

Best Mode for Carrying Out the Invention

In the compound of the present invention represented by the aforementioned formula (I), it is important to contain at least one amine structure as symbol "Z", isoindoline ring or tetrahydroisoquinoline ring for the group represented by formula:



The amine structure may be primary amine, secondary amine, tertiary amine, ammonium salt or ring amine. And the number of amine structures in the compounds may be preferably two or more.

The "alkyl group" or an alkyl portion of a functional group containing the alkyl portion (alkoxyl group, for example) used herein may be linear, branched, cyclic or a combination thereof. The "C_1-C_{15} alkyl group" used herein may be, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, isopentyl group, neopentyl group, tert-pentyl group, n-hexyl group, isohexyl group, or a linear or branched heptyl group, octyl group, nonyl group, decyl group, undecyl group, dodecyl group, tridecyl group, tetradecyl group or pentadecyl group, or cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, cyclooctyl group, cyclopropylmethyl group, cyclobutylmethyl group, cyclohexylmethyl group or the like. In the specification, when a functional group is defined as "which may be substituted" or "optionally substituted", the number of substituents as well as their types and substituting positions are not particularly limited, and when two or more substituents are present, they may be the same or different.

When the alkyl group has one or more substituents, the alkyl group may have one or more substituents "M" selected form the group consisting of a halogen atom (the term "halogen" used herein may mean any of fluorine atom, chlorine atom, bromine atom, and iodine atom); a C_1-C_{15} halogenated alkyl group such as trifluoromethyl group, trifluorethyl group and pentafluoroethyl group; a C_1-C_{15} alkyloxy group such as methoxy group, ethoxy group, n-propoxy group, isopropoxy group, n-butoxy group, isobutoxy group, tert-butoxy group, n-pentyloxy group, isopentyloxy group, tert-pentyloxy group, hexyloxy group, cyclopropyloxy group, cyclobutyloxy group, cyclopentyloxy group, cyclohexyloxy group, cycloheptyloxy group, and cyclooctyloxy group; a C_1-C_{15} alkylthio group such as methylthio group, ethylthio

group, propylthio group, butylthio group, pentylthio group and hexylthio group; a C_1-C_5 alkylenedioxy group such as methylenedioxy group, ethylenedioxy group, and propylenedioxy group; hydroxyl group; a C_2-C_6 alkylcarbonyloxy group such as acetoxy group, propionyloxy group, butyryloxy group, and valeryloxy group; carboxyl group; a C_2-C_6 alkoxycarbonyl group such as methoxycarbonyl group, ethoxycarbonyl group, n-propoxycarbonyl group, isopropoxycarbonyl group, butoxycarbonyl group, isobutoxycarbonyl group, tert-butoxycarbonyl group, pentyloxycarbonyl group, and isopentyloxycarbonyl group; oxo group; a C_2-C_6 alkylcarbonyl group such as acetyl group, propionyl group, butyryl group, and valeryl group; C_7-C_{13} arylcarbonyl group such as benzoyl group or naphthoyl group; amino group; a monoalkylamino group which may be substituted with a C_1-C_{15} alkyl group; a dialkylamino group which may be substituted with the same or different C_1-C_{15} alkyl groups; a C_2-C_6 alkylcarbonylamino group such as acetylamino group, propionylamino group, isopropionylamino group, butyrylamino group, and valerylamino group; carbamoyl group; a C_2-C_6 alkylcarbamoyl group such as methylcarbamoyl group, ethylcarbamoyl group, propylcarbamoyl group, butylcarbamoyl group, tert-butylcarbamoyl group, and pentylcarbamoyl group; nitro group; cyano group; a C_6-C_{12} aryl group such as phenyl group, and naphthyl group; fluorenyl group; a C_6-C_{12} aryloxy group such as phenoxy group, and naphthoxy group; a C_6-C_{12} arylthio group such as phenylthio group or naphthylthio group; and a heterocyclic group.

Examples of "alkyl group having from 1 to 5 carbon atoms" used herein include, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, isopentyl group, neopentyl group, tert-pentyl group and the like and examples of "alkoxyl group having from 1 to 5 carbon atoms" include, for example, methoxy group, ethoxy group, n-propoxy group, isopropoxy group, n-butoxy group, isobutoxy group, tert-butoxy group, n-pentyloxy group, isopentyloxy group and the like, and examples

of "alkylene group having from 1 to 5 carbon atoms" used herein include, for example, methylene group, ethylene group, propylene group, trimethylene group, tetramethylene group and the like.

The term "heterocyclic group" used herein means a residue of heterocyclic ring having 1-4 heteroatoms selected from oxygen atom, sulfur atom, and nitrogen atom, and having total ring-constituting atoms of 5 to 10, and its bonding position is not particularly limited. Preferred heterocyclic group of the compounds includes a residue of monocyclic heterocyclic ring having 1-4 heteroatoms selected from oxygen atom, sulfur atom, and nitrogen atom, and having total ring-constituting atoms of 5 to 7. More specifically, examples include, for example, residues of furan ring, dihydrofuran ring, tetrahydrofuran ring, pyran ring, dihydropyran ring, tetrahydropyran ring, thiophene ring, pyrrole ring, pyrroline ring, pyrrolidine ring, imidazole ring, imidazoline ring, imidazolidine ring, pyrazole ring, pyrazoline ring, pyrazolidine ring, triazole ring, tetrazole ring, pyridine ring, pyridine oxide ring, piperidine ring, azepine, dihydroazepine, tetrahydroazepine, pyrazine ring, piperazine ring, homopiperazine ring, pyrimidine ring, pyridazine ring, oxazole ring, oxazolidine ring, isoxazole ring, isoxazolidine ring, thiazole ring, thiazylidine ring, isothiazole ring, isothiazolidine ring, dioxane ring, dithian ring, morpholine ring, thiomorpholine ring and the like. These residues may form a bonding at any position on the ring.

The term "aryl group having 6 to 12 carbon atoms (C_6-C_{12} aryl group)" include, for example, 6 to 12-membered monocyclic or bicyclic aryl groups, and examples include phenyl group, naphthyl group and the like. The bonding position of the aryl group is not particularly limited, and the aryl group may form a bonding at any position on the ring. When the aryl group has one or more substituents, the aryl group may have one or more substituents "N" selected from the group consisting of a C_1-C_{15} alkyl group; an aralkyl group having from 7 to 14 carbon atoms such as benzyl

group, phenethyl group, phenylpropyl group, naphthylmethyl group and naphthylethyl group; and the aforementioned groups "M" that may substitute on the alkyl group.

When the heterocyclic group has one or more substituents, the heterocyclic group may have one or more substituents selected from the group "N".

The term "nitrogen-containing heterocyclic group" used herein means a heterocyclic group containing one or more nitrogen atoms as ring-constituting atoms which may further have one or more heteroatoms such as oxygen atom and sulfur atom. Preferred nitrogen-containing heterocyclic group includes non-aromatic monocyclic heterocyclic group having total ring-constituting atoms of 4 to 7. Examples of the heterocyclic ring include, for example, azetidine ring, pyrrolidine ring, pyrroline ring, imidazolidine ring, imidazoline ring, pyrazolidine ring, pyrazoline ring, piperidine ring, piperadine ring, homopiperadine ring, dihydroazepine ring, tetrahydroazepine ring, morpholine ring, thiomorpholine ring, thiazylidine ring, isothiazolidine ring, oxazolidine ring, isoxazolidine ring and the like. When the nitrogen-containing heterocyclic group has one or more substituents, the heterocyclic group may have one or more substituents selected from the group "N".

The nitrogen-containing heterocyclic group having one or more sp^2 nitrogen atoms represented by Z preferably includes monocyclic heterocyclic ring having total ring-constituting atoms of 5 to 7 which may further have one or more heteroatoms such as oxygen atom and sulfur atom. More specifically, examples include, for example, residues of 2H-pyrrole ring, imidazole ring, pyrazole ring, isoxazole ring, isothiazole ring, pyridine ring, pyrazine ring, pyrimidine ring, pyridazine ring, azepine and the like. When the nitrogen-containing heterocyclic group having one or more sp^2 nitrogen atoms has one or more substituents, the heterocyclic group may have one or more substituents selected from the group "N".

The alkyl group, aryl group, and heterocyclic group explained above as for the

substituents "N" may further have one or more substituents selected from the group consisting of a halogen atom; a C_1-C_{15} alkyl group; a C_7-C_{14} aralkyl group; a C_1-C_{15} halogenated alkyl group; a C_1-C_{15} alkoxyl group; a C_1-C_{15} alkylthio group; a C_1-C_5 alkylenedioxy group; hydroxyl group; a C_2-C_6 alkylcarbonyloxy group; carboxyl group; a C_2-C_6 alkoxycarbonyl group; oxo group; a C_2-C_6 alkylcarbonyl group; a C_7-C_{13} arylcarbonyl group; amino group; a monoalkylamino group substituted with a C_1-C_{15} alkyl group; a dialkylamino group substituted with the same or different C_1-C_{15} alkyl groups; a C_2-C_6 alkylcarbonylamino group; carbamoyl group; a C_2-C_6 alkylcarbamoyl group; nitro group; cyano group; a C_6-C_{12} aryl group; fluorenyl group; a C_6-C_{12} aryloxy group; a C_6-C_{12} arylthio group, and a heterocyclic group.

In the aforementioned groups, preferable examples of 2-hydroxybenzimidazolyl group which may be substituted or 2-hydroxynaphthoimidazolyl group which may be substituted represented by R^1 include said groups which is non-substituted, or said groups having one or two halogen atoms or one or two alkyl groups. 2-Hydroxybenzimidazolyl group, 5,6-dichloro-2-hydroxybenzimidazolyl group, and 2-hydroxynaphthoimidazolyl group are especially preferable. Y may preferably be oxygen atom and symbol "n" may preferably be 0 or 1. X^1 and X^5 may preferably be hydrogen atoms.

Examples of preferred compounds of the present invention include, for example,

N-(4-(4-piperidyl)methylaminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazol-1-carboxyamide;

N-(4-(4-aminomethyl-1-pyperidinylmethyl)phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide;

N-(4-(4-(2-aminoethyl)-1-pyperadinylmethyl)phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide;

N-(4-(((3-pyperidinylmethyl)amino)methyl)phenyl)-5,6-dichloro-2-hydroxy-1H-benz-

imidazole-1-carboxamide;

N-(4-(4-dimethylaminomethyl-1-pyperidinylmethyl)phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide;

N-(4-(4-(2-dimethylaminoethyl)-1-pyperidinylmethyl)phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide;

N-(4-((4-aminobutylamino)methyl)phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide;

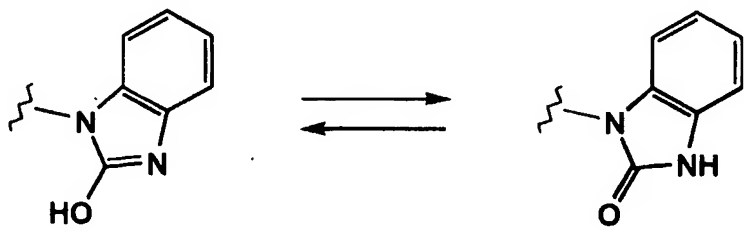
N-(4-((N-methyl-N-(4-methylaminocyclohexyl)) amino) methyl) phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide and the like.

In addition to the compounds represented by the aforementioned formula (I), physiologically acceptable salts thereof may be used as the active ingredient of the medicament of the present invention. Examples of the salt include, when an acidic group exists, salts of alkali metals and alkaline earth metals such as lithium, sodium, potassium, magnesium, and calcium; salts of ammonia and amines such as methylamine, dimethylamine, trimethylamine, dicyclohexylamine, tris(hydroxymethyl)aminomethane, N,N-bis(hydroxyethyl)piperazine, 2-amino-2-methyl-1-propanol, ethanolamine, N-methylglucamine, and L-glucamine; or salts with basic amino acids such as lysine, δ-hydroxylysine, and arginine. When a basic group exists, examples include salts with mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, and phosphoric acid; salts with organic acids such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, acetic acid, propionic acid, tartaric acid, fumaric acid, maleic acid, malic acid, oxalic acid, succinic acid, citric acid, benzoic acid, mandelic acid, cinnamic acid, lactic acid, glycolic acid, glucuronic acid, ascorbic acid, nicotinic acid, and salicylic acid; or salts with acidic amino acids such as aspartic acid, and glutamic acid. Furthermore, when a quaternary nitrogen atom exists in a molecule, any anion may be attached as a pair ion. Examples of the ion include, for example, a halogenide ion such as fluoride ion,

chloride ion, bromide ion and iodide ion; diphenylphosphoryl ion and hydroxide ion and the like.

Solvates and hydrates of the carboxyamido derivatives represented by the aforementioned formula (I) and salts thereof may also be used as the active ingredient of the medicament of the present invention. Furthermore, the carboxyamido derivatives represented by the aforementioned formula (I) may have one or more asymmetric carbon atoms. As for the stereochemistry of such asymmetric carbon atoms, they may independently be in either (R), (S) or (RS) configuration, and the carboxyamido derivatives may exist as stereoisomers such as optical isomers, or diastereoisomers. Any stereoisomers of pure form, any mixtures of stereoisomers, racemates and the like may be used as the active ingredient of the medicament of the present invention.

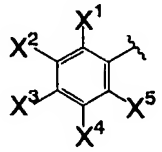
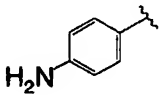
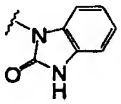
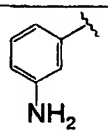
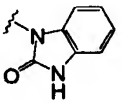
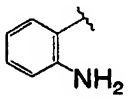
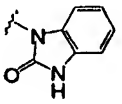
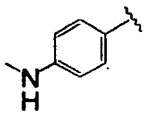
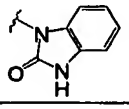
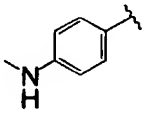
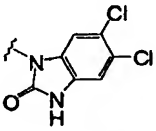
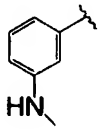
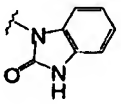
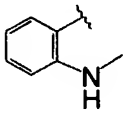
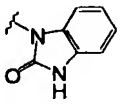
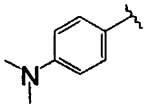
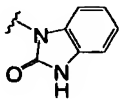
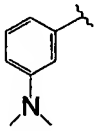
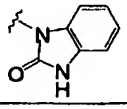
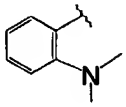
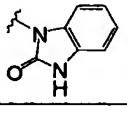
Furthermore, it is well known that a ketone compound may exist as a tautomer of the 2-hydroxybenzimidazolyl group and 2-hydroxynaphthoimidazolyl group represented by R^1 in the formula (I). Accordingly, benzimidazolidine-2-one and naphthoimidazolidine-2-one which are the tautomer of 2-hydroxy-type also fall within the scope of the present invention.



Hydroxyl-type Ketone-type

Examples of preferred compounds of the present invention are shown in the tables below. However, the scope of the present invention is not limited by the following compounds.

Table-1

Compound Number		n	R^2	Y	R^1
1		0	H	O	
2		0	H	O	
3		0	H	O	
4		0	H	O	
5		0	H	O	
6		0	H	O	
7		0	H	O	
8		0	H	O	
9		0	H	O	
10		0	H	O	

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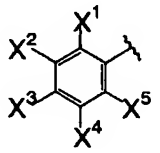
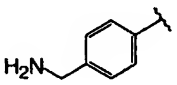
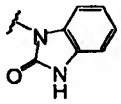
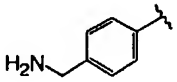
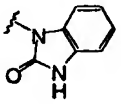
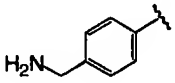
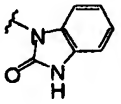
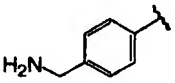
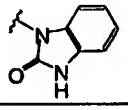
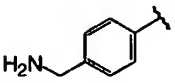
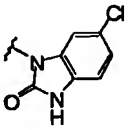
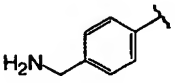
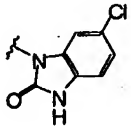
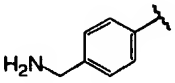
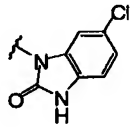
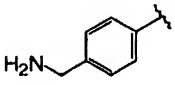
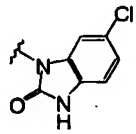
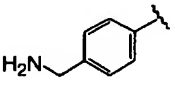
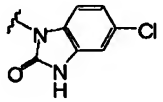
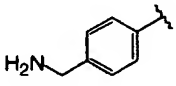
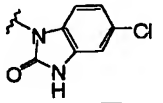
Compound Number		n	R^2	Y	R^1
11		0	H	O	
12		0	H	S	
13		1	H	O	
14		1	H	S	
15		0	H	O	
16		0	H	S	
17		1	H	O	
18		1	H	S	
19		0	H	O	
20		0	H	S	

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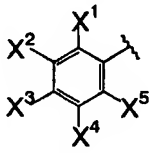
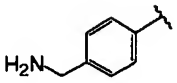
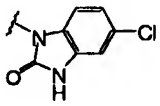
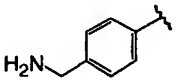
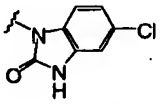
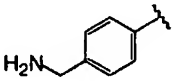
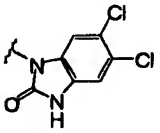
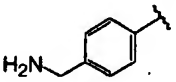
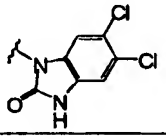
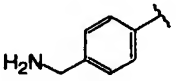
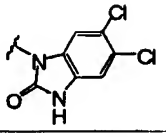
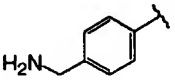
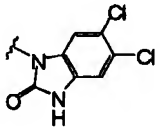
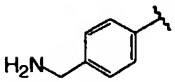
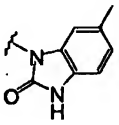
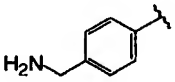
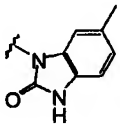
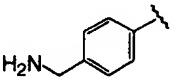
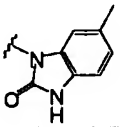
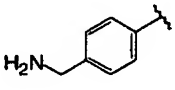
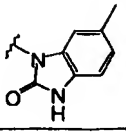
Compound Number		n	R^2	Y	R^1
21		1	H	O	
22		1	H	S	
23		0	H	O	
24		0	H	S	
25		1	H	O	
26		1	H	S	
27		0	H	O	
28		0	H	S	
29		1	H	O	
30		1	H	S	

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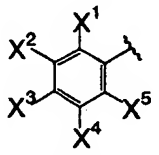
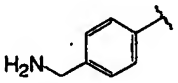
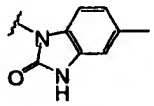
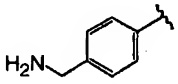
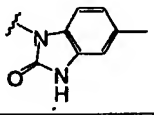
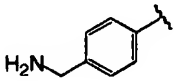
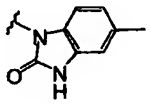
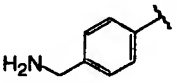
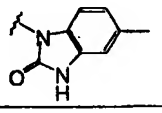
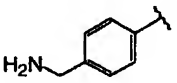
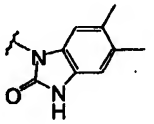
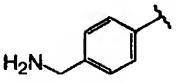
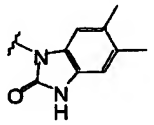
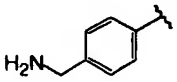
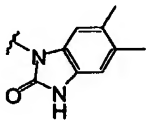
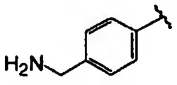
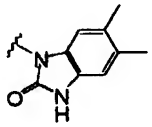
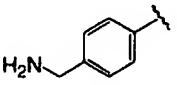
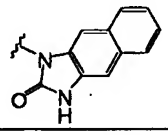
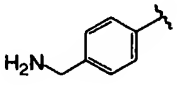
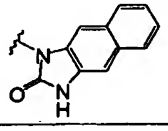
Compound Number		n	R^2	Y	R^1
31		0	H	O	
32		0	H	S	
33		1	H	O	
34		1	H	S	
35		0	H	O	
36		0	H	S	
37		1	H	O	
38		1	H	S	
39		0	H	O	
40		0	H	S	

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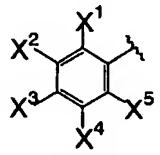
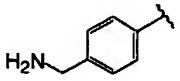
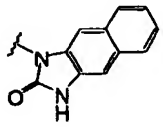
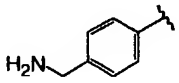
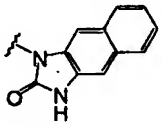
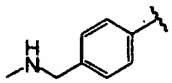
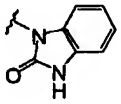
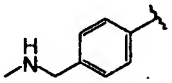
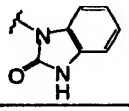
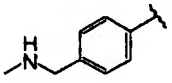
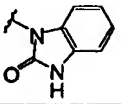
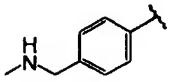
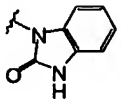
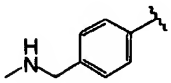
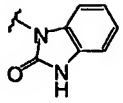
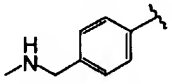
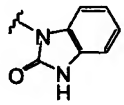
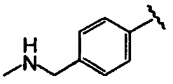
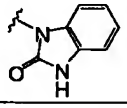
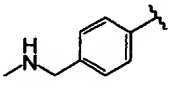
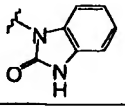
Compound Number		n	R^2	Y	R^1
41		1	H	O	
42		1	H	S	
43		0	H	O	
44		0	H	S	
45		1	H	O	
46		1	H	S	
47		2	H	O	
48		2	H	S	
49		0	CH_3	O	
50		0	CH_3	S	

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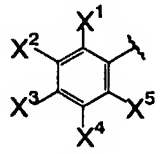
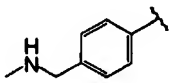
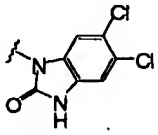
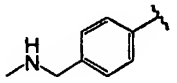
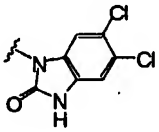
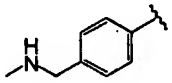
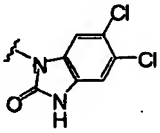
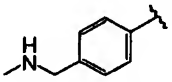
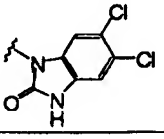
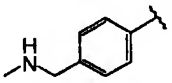
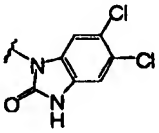
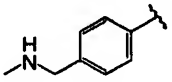
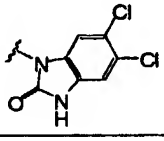
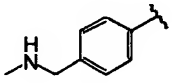
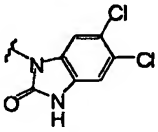
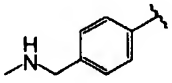
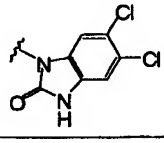
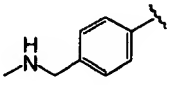
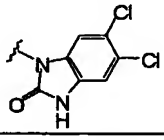
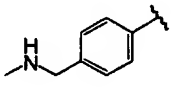
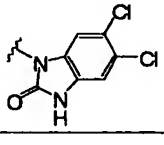
Compound Number		n	R^2	Y	R^1
51		0	H	O	
52		0	H	S	
53		1	H	O	
54		1	H	S	
55		2	H	O	
56		2	H	S	
57		0	CH_3	O	
58		0	CH_3	S	
59		1	CH_3	O	
60		1	CH_3	S	

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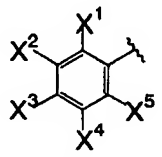
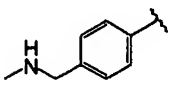
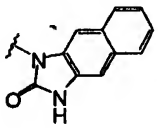
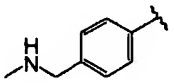
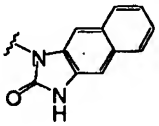
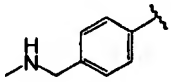
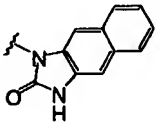
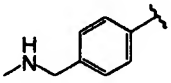
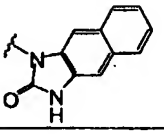
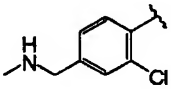
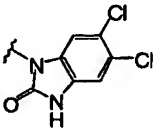
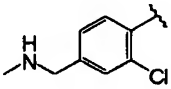
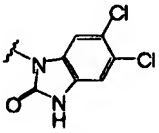
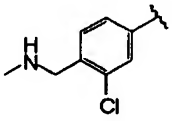
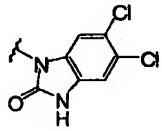
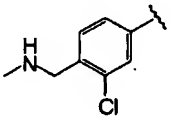
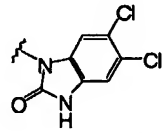
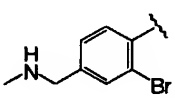
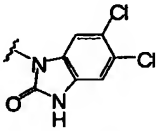
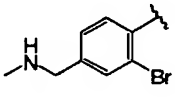
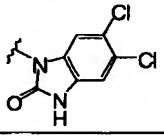
Compound Number		n	R^2	Y	R^1
61		0	H	O	
62		0	H	S	
63		1	H	O	
64		1	H	S	
65		0	H	O	
66		0	H	S	
67		0	H	O	
68		0	H	S	
69		0	H	O	
70		0	H	S	

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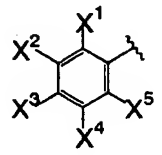
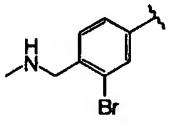
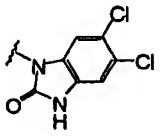
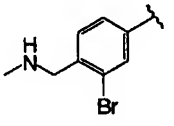
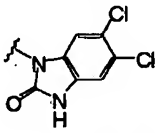
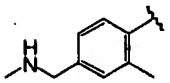
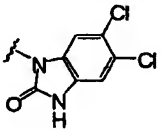
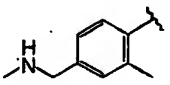
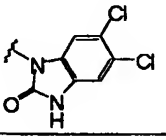
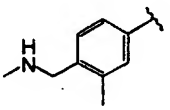
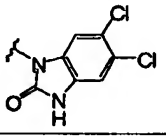
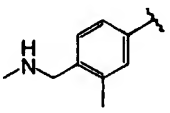
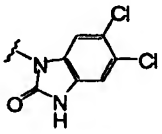
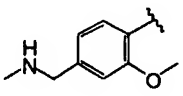
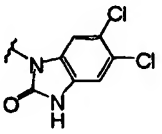
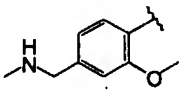
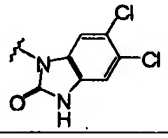
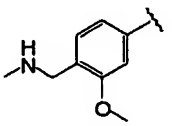
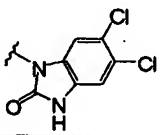
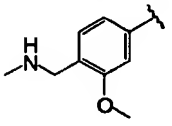
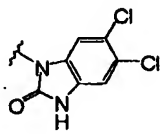
Compound Number		n	R^2	Y	R^1
71		0	H	O	
72		0	H	S	
73		0	H	O	
74		1	H	O	
75		0	H	O	
76		1	H	O	
77		0	H	O	
78		1	H	O	
79		0	H	O	
80		1	H	O	

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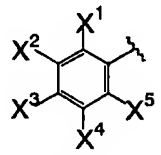
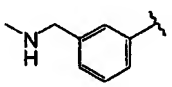
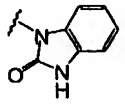
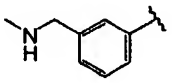
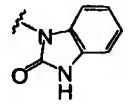
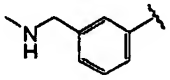
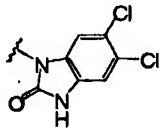
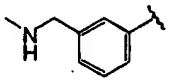
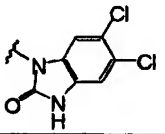
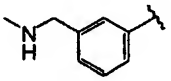
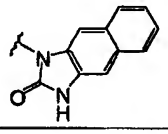
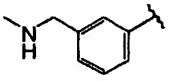
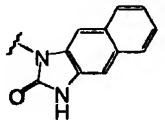
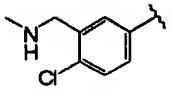
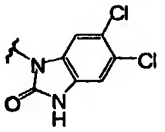
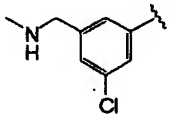
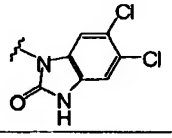
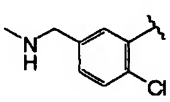
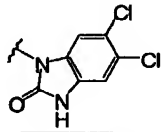
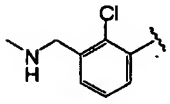
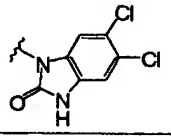
Compound Number		n	R^2	Y	R^1
81		0	H	O	
82		1	H	O	
83		0	H	O	
84		1	H	O	
85		0	H	O	
86		1	H	O	
87		0	H	O	
88		0	H	O	
89		0	H	O	
90		0	H	O	

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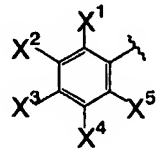
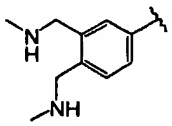
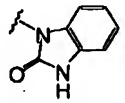
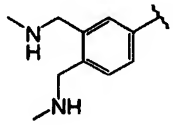
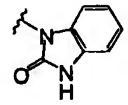
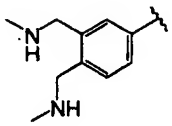
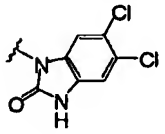
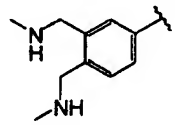
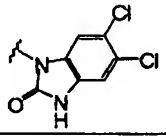
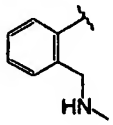
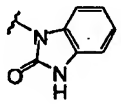
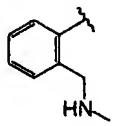
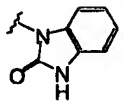
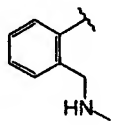
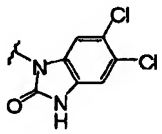
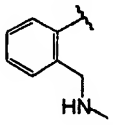
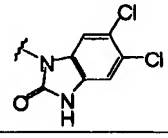
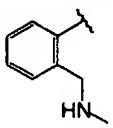
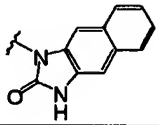
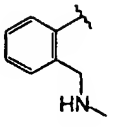
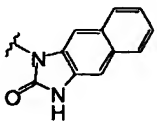
Compound Number		n	R^2	Y	R^1
91		0	H	O	
92		1	H	O	
93		0	H	O	
94		1	H	O	
95		0	H	O	
96		1	H	O	
97		0	H	O	
98		1	H	O	
99		0	H	O	
100		1	H	O	

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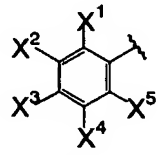
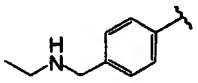
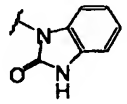
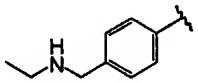
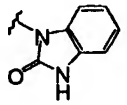
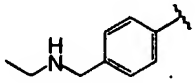
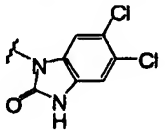
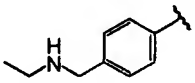
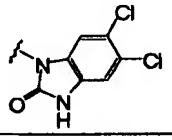
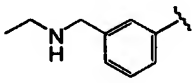
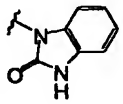
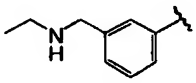
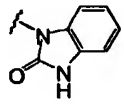
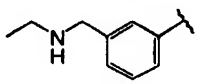
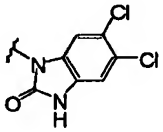
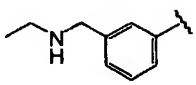
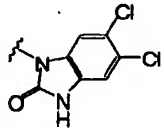
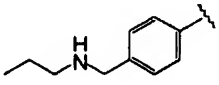
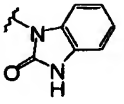
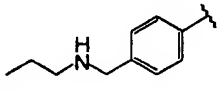
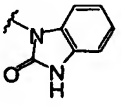
Compound Number		n	R^2	Y	R^1
101		0	H	O	
102		1	H	O	
103		0	H	O	
104		1	H	O	
105		0	H	O	
106		1	H	O	
107		0	H	O	
108		1	H	O	
109		0	H	O	
110		1	H	O	

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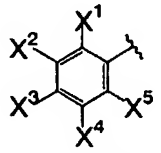
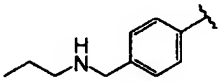
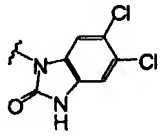
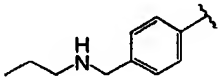
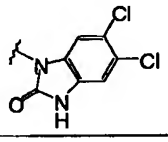
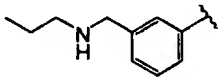
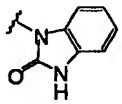
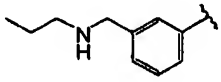
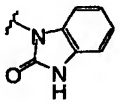
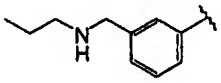
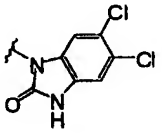
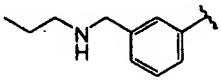
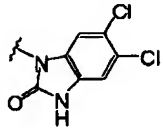
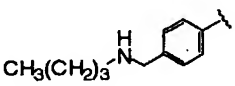
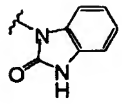
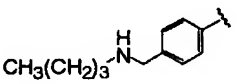
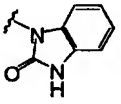
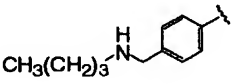
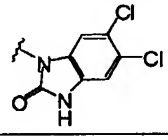
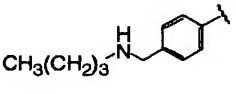
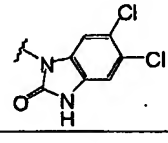
Compound Number		n	R^2	Y	R^1
111		0	H	O	
112		1	H	O	
113		0	H	O	
114		1	H	O	
115		0	H	O	
116		1	H	O	
117		0	H	O	
118		1	H	O	
119		0	H	O	
120		1	H	O	

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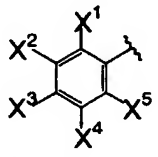
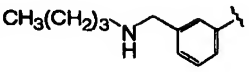
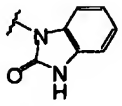
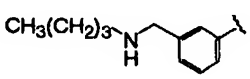
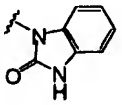
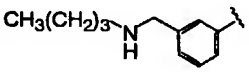
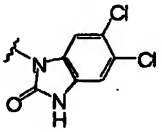
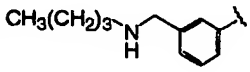
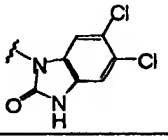
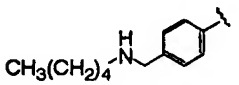
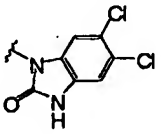
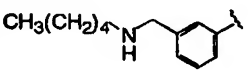
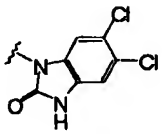
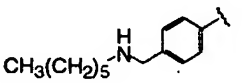
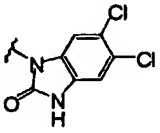
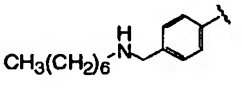
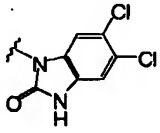
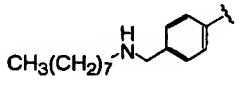
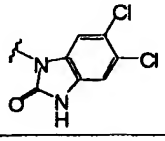
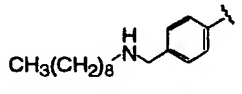
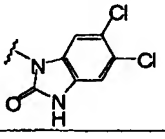
Compound Number		n	R^2	Y	R^1
121		0	H	O	
122		1	H	O	
123		0	H	O	
124		1	H	O	
125		0	H	O	
126		0	H	O	
127		0	H	O	
128		0	H	O	
129		0	H	O	
130		0	H	O	

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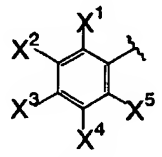
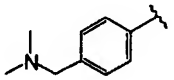
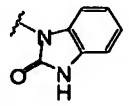
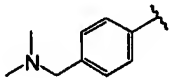
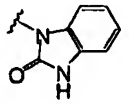
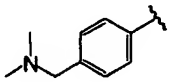
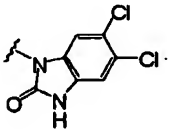
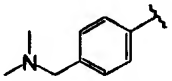
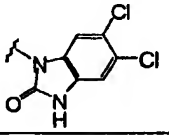
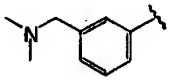
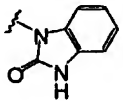
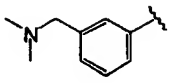
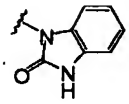
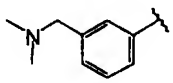
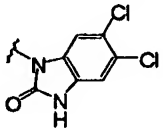
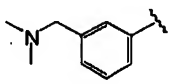
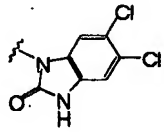
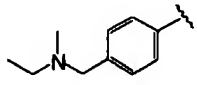
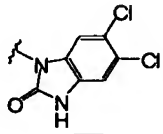
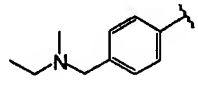
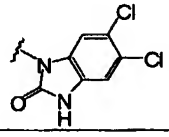
Compound Number		n	R^2	Y	R^1
131		0	H	O	
132		1	H	O	
133		0	H	O	
134		1	H	O	
135		0	H	O	
136		1	H	O	
137		0	H	O	
138		1	H	O	
139		0	H	O	
140		1	H	O	

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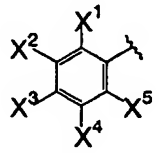
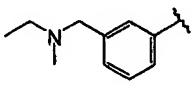
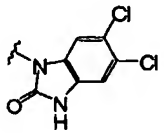
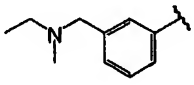
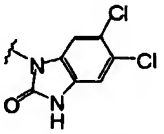
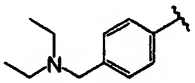
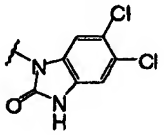
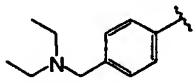
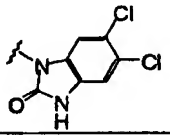
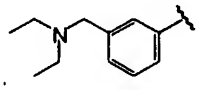
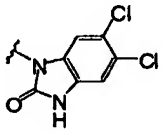
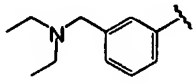
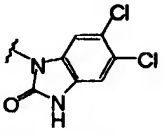
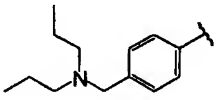
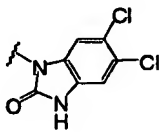
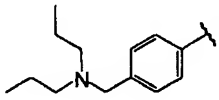
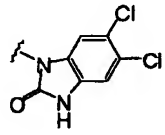
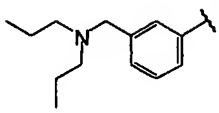
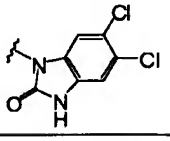
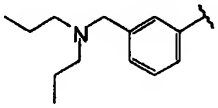
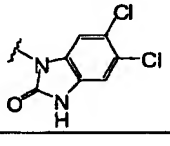
Compound Number		n	R^2	Y	R^1
141		0	H	O	
142		1	H	O	
143		0	H	O	
144		1	H	O	
145		0	H	O	
146		1	H	O	
147		0	H	O	
148		1	H	O	
149		0	H	O	
150		1	H	O	

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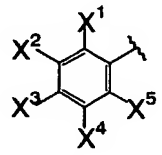
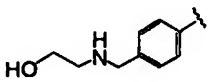
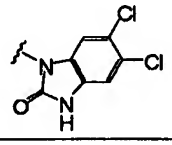
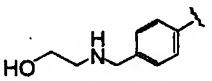
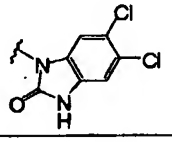
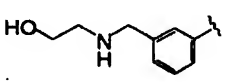
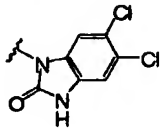
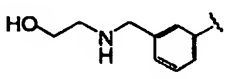
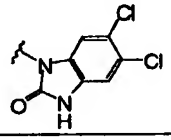
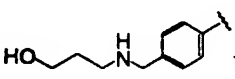
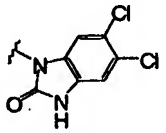
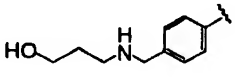
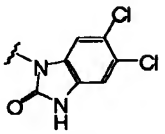
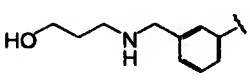
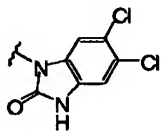
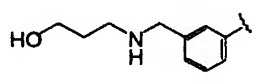
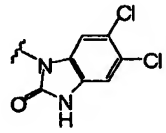
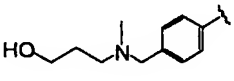
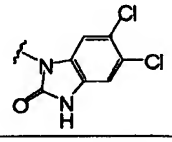
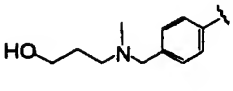
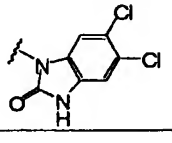
Compound Number		n	R^2	Y	R^1
151		0	H	O	
152		1	H	O	
153		0	H	O	
154		1	H	O	
155		0	H	O	
156		1	H	O	
157		0	H	O	
158		1	H	O	
159		0	H	O	
160		1	H	O	

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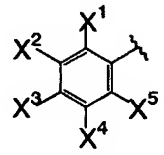
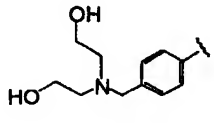
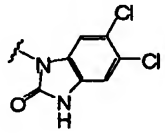
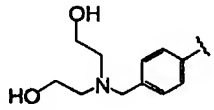
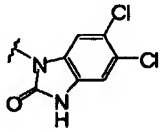
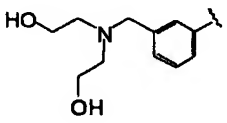
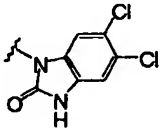
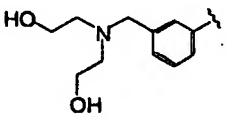
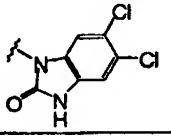
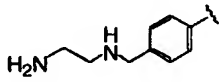
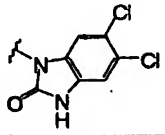
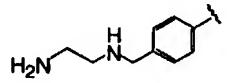
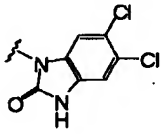
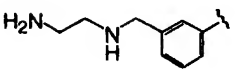
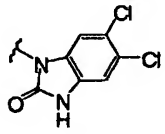
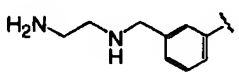
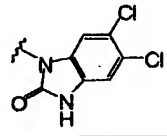
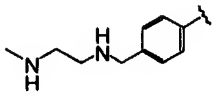
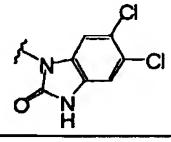
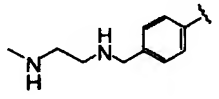
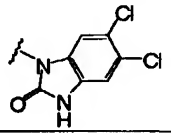
Compound Number		n	R^2	Y	R^1
161		0	H	O	
162		1	H	O	
163		0	H	O	
164		1	H	O	
165		0	H	O	
166		1	H	O	
167		0	H	O	
168		1	H	O	
169		0	H	O	
170		1	H	O	

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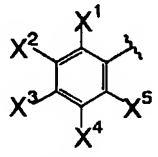
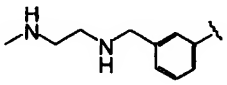
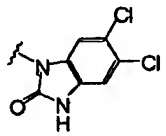
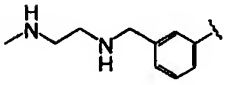
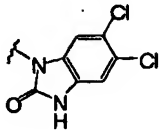
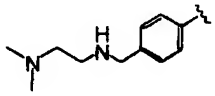
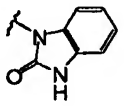
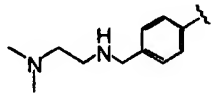
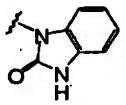
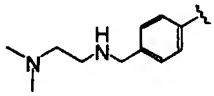
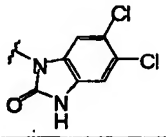
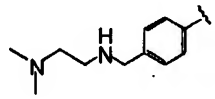
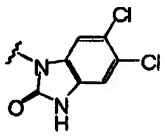
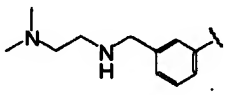
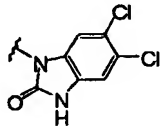
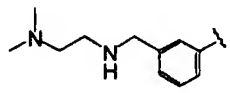
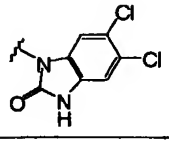
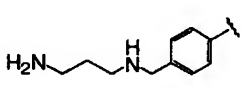
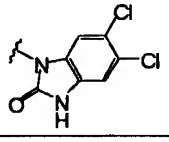
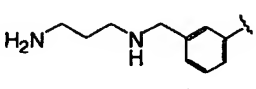
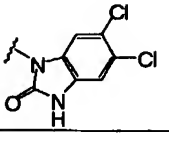
Compound Number		n	R^2	Y	R^1
171		0	H	O	
172		1	H	O	
173		0	H	O	
174		1	H	O	
175		0	H	O	
176		1	H	O	
177		0	H	O	
178		1	H	O	
179		0	H	O	
180		0	H	O	

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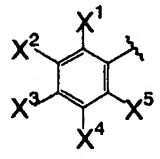
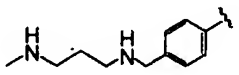
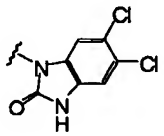
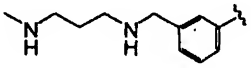
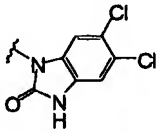
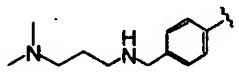
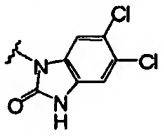
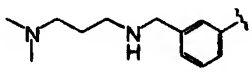
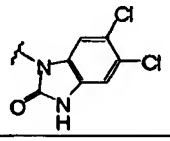
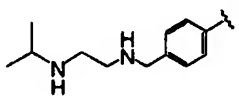
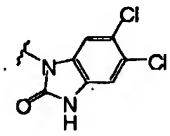
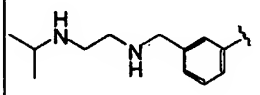
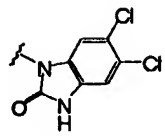
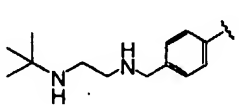
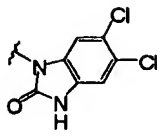
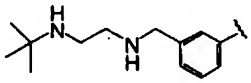
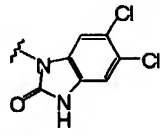
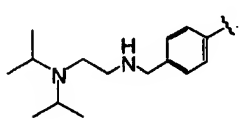
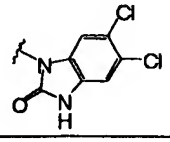
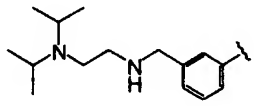
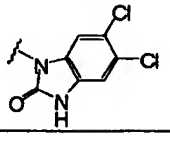
Compound Number		n	R^2	Y	R^1
181		0	H	O	
182		0	H	O	
183		0	H	O	
184		0	H	O	
185		0	H	O	
186		0	H	O	
187		0	H	O	
188		0	H	O	
189		0	H	O	
190		0	H	O	

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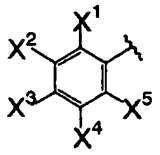
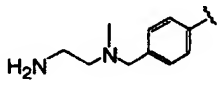
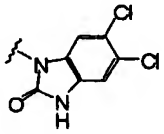
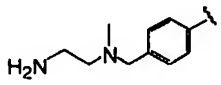
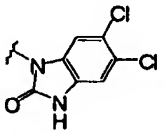
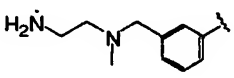
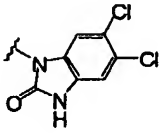
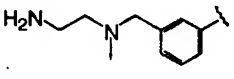
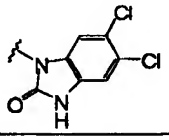
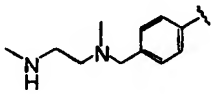
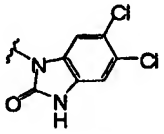
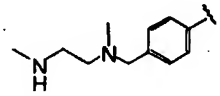
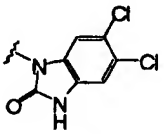
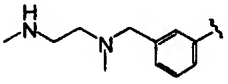
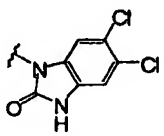
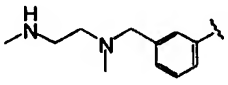
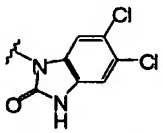
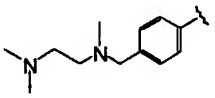
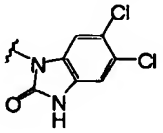
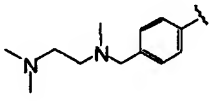
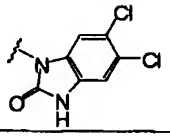
Compound Number		n	R^2	Y	R^1
191		0	H	O	
192		1	H	O	
193		0	H	O	
194		1	H	O	
195		0	H	O	
196		1	H	O	
197		0	H	O	
198		1	H	O	
199		0	H	O	
200		1	H	O	

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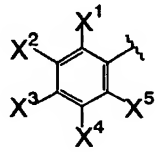
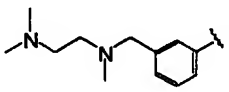
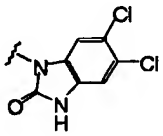
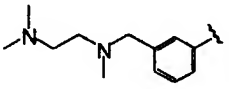
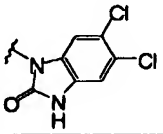
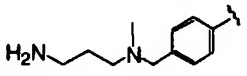
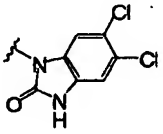
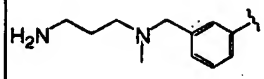
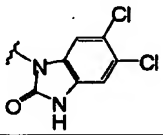
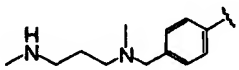
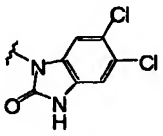
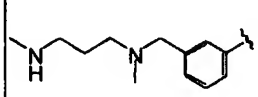
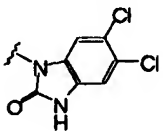
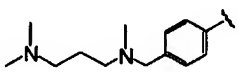
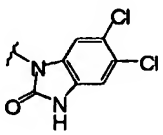
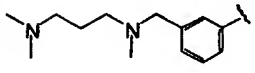
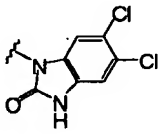
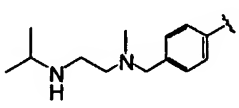
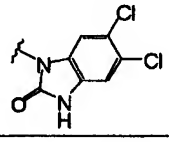
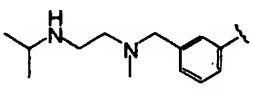
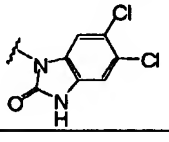
Compound Number		n	R^2	Y	R^1
201		0	H	O	
202		1	H	O	
203		0	H	O	
204		0	H	O	
205		0	H	O	
206		0	H	O	
207		0	H	O	
208		0	H	O	
209		0	H	O	
210		0	H	O	

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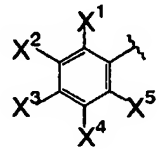
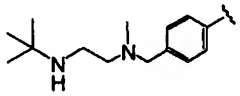
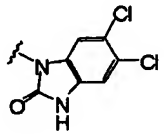
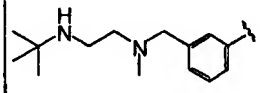
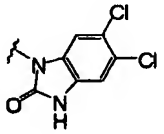
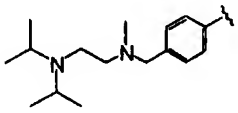
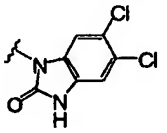
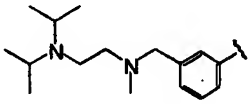
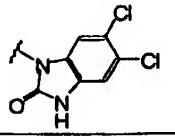
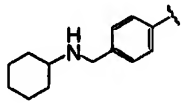
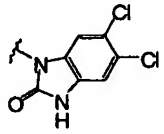
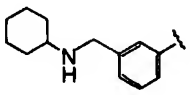
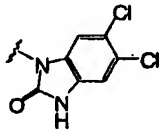
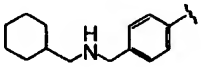
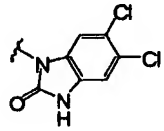
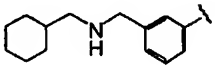
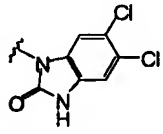
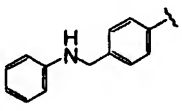
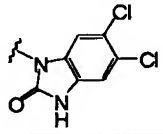
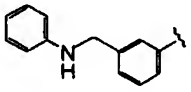
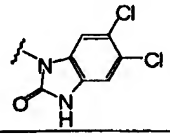
Compound Number		n	R^2	Y	R^1
211		0	H	O	
212		0	H	O	
213		0	H	O	
214		0	H	O	
215		0	H	O	
216		0	H	O	
217		0	H	O	
218		0	H	O	
219		0	H	O	
220		0	H	O	

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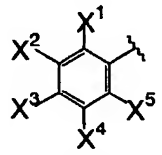
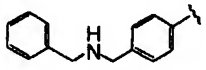
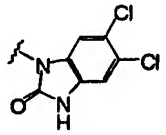
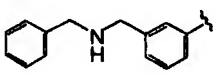
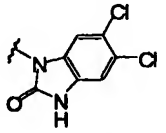
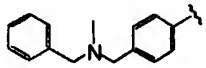
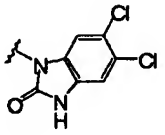
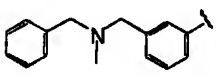
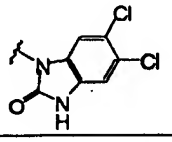
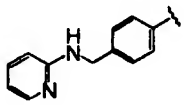
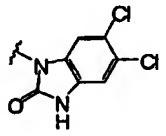
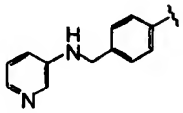
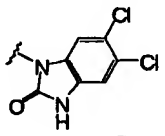
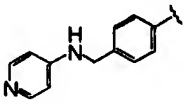
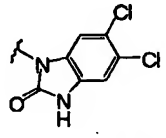
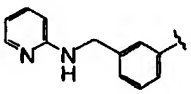
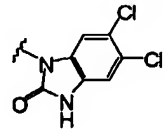
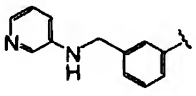
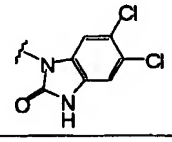
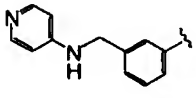
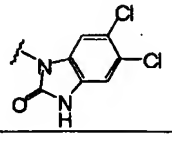
Compound Number		n	R^2	Y	R^1
221		0	H	O	
222		0	H	O	
223		0	H	O	
224		0	H	O	
225		0	H	O	
226		0	H	O	
227		0	H	O	
228		0	H	O	
229		0	H	O	
230		0	H	O	

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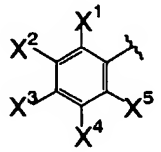
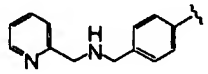
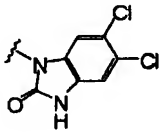
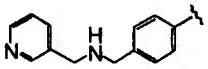
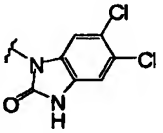
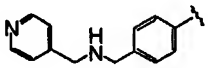
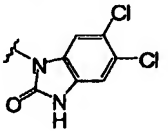
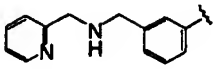
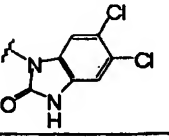
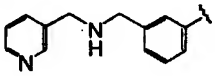
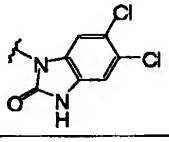
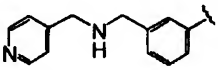
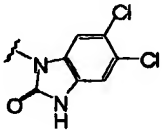
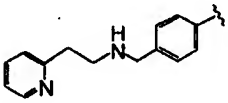
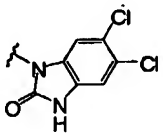
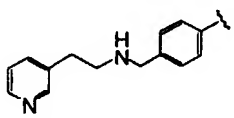
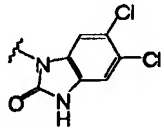
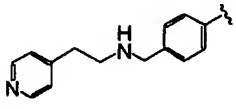
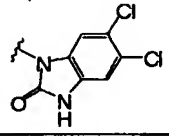
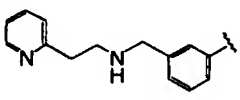
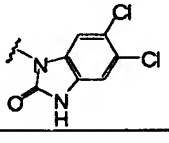
Compound Number		n	R^2	Y	R^1
231		0	H	O	
232		0	H	O	
233		0	H	O	
234		0	H	O	
235		0	H	O	
236		0	H	O	
237		0	H	O	
238		0	H	O	
239		0	H	O	
240		0	H	O	

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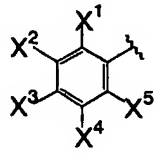
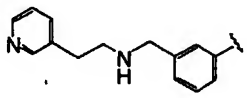
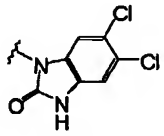
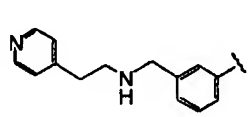
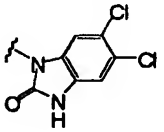
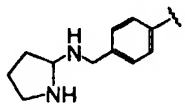
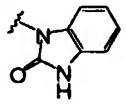
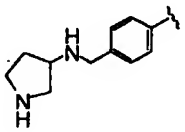
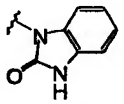
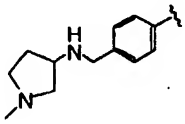
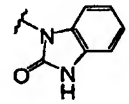
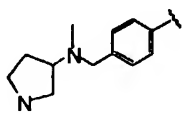
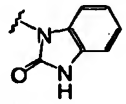
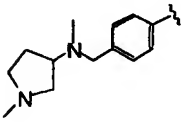
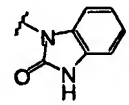
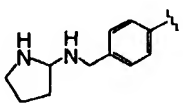
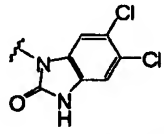
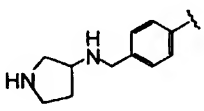
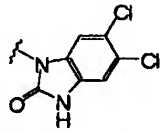
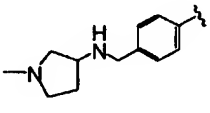
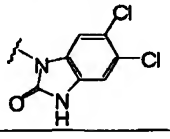
Compound Number		n	R^2	Y	R^1
241		0	H	O	
242		0	H	O	
243		0	H	O	
244		0	H	O	
245		0	H	O	
246		0	H	O	
247		0	H	O	
248		0	H	O	
249		0	H	O	
250		0	H	O	

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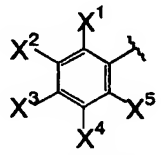
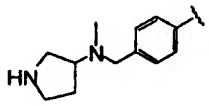
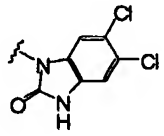
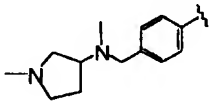
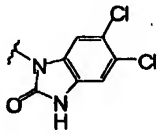
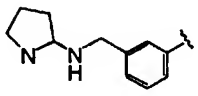
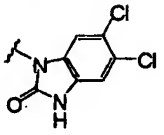
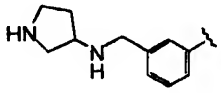
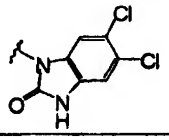
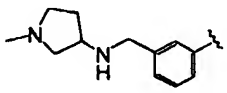
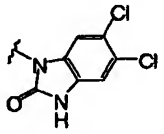
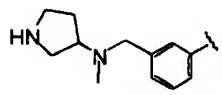
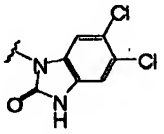
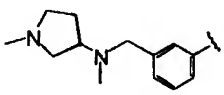
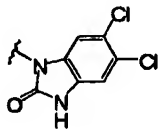
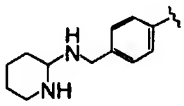
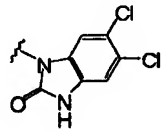
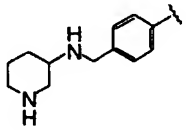
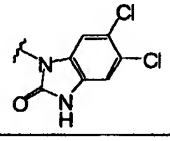
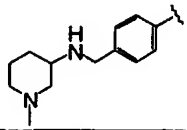
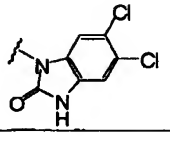
Compound Number		n	R^2	Y	R^1
251		0	H	O	
252		0	H	O	
253		0	H	O	
254		0	H	O	
255		0	H	O	
256		0	H	O	
257		0	H	O	
258		0	H	O	
259		0	H	O	
260		0	H	O	

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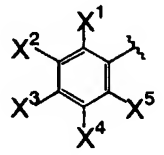
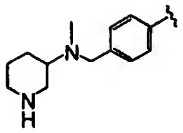
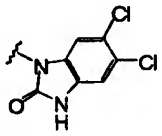
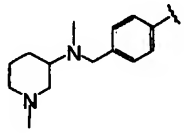
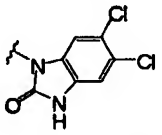
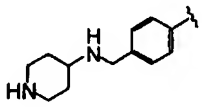
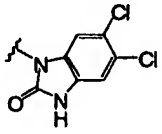
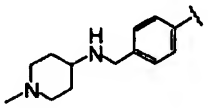
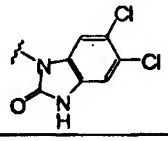
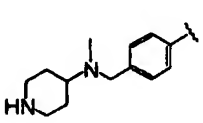
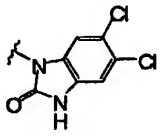
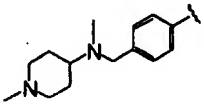
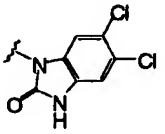
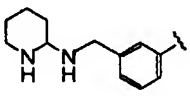
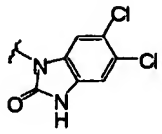
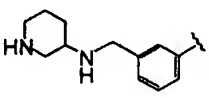
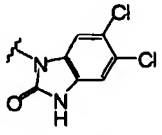
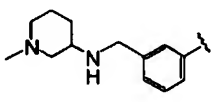
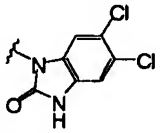
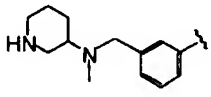
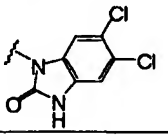
Compound Number		n	R^2	Y	R^1
261		0	H	O	
262		0	H	O	
263		0	H	O	
264		0	H	O	
265		0	H	O	
266		0	H	O	
267		0	H	O	
268		0	H	O	
269		0	H	O	
270		0	H	O	

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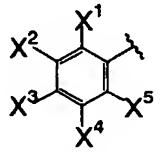
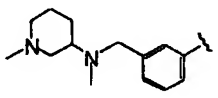
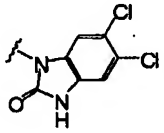
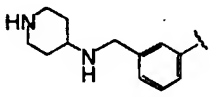
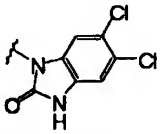
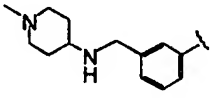
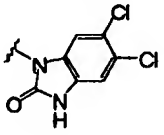
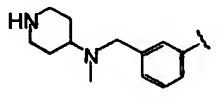
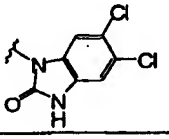
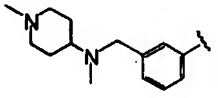
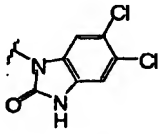
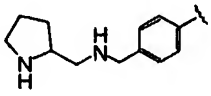
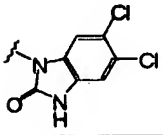
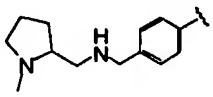
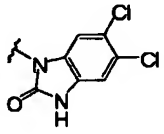
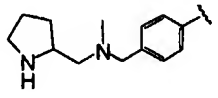
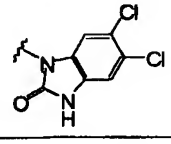
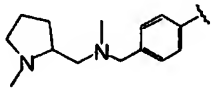
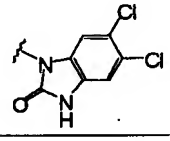
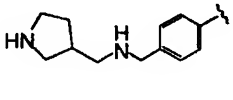
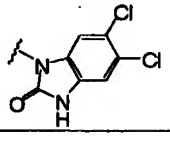
Compound Number		n	R^2	Y	R^1
271		0	H	O	
272		0	H	O	
273		0	H	O	
274		0	H	O	
275		0	H	O	
276		0	H	O	
277		0	H	O	
278		0	H	O	
279		0	H	O	
280		0	H	O	

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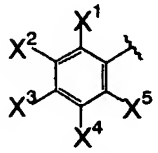
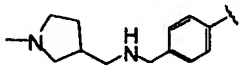
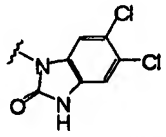
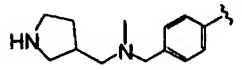
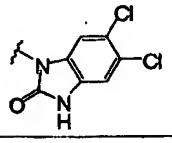
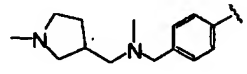
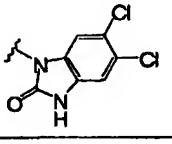
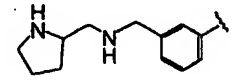
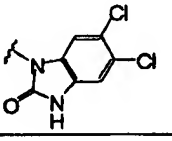
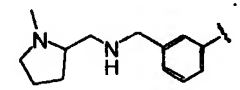
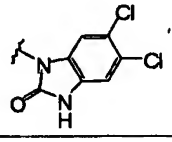
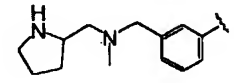
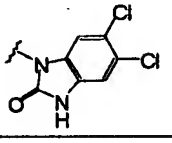
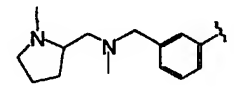
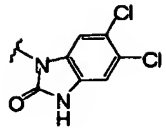
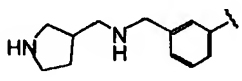
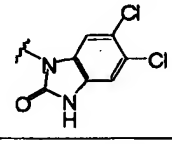
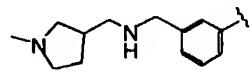
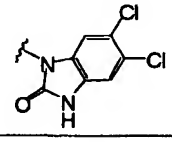
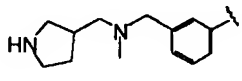
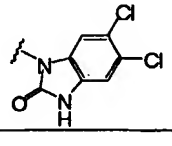
Compound Number		n	R^2	Y	R^1
281		0	H	O	
282		0	H	O	
283		0	H	O	
284		0	H	O	
285		0	H	O	
286		0	H	O	
287		0	H	O	
288		0	H	O	
289		0	H	O	
290		0	H	O	

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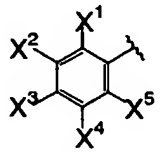
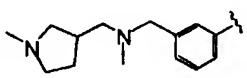
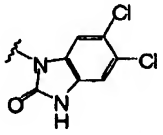
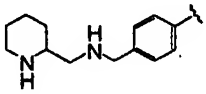
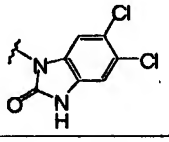
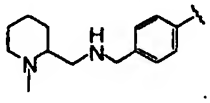
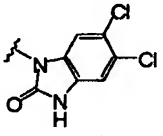
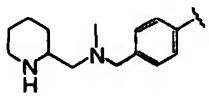
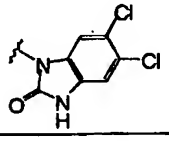
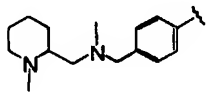
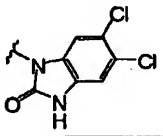
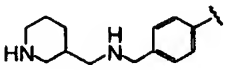
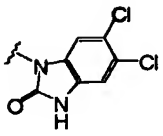
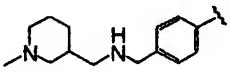
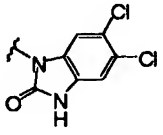
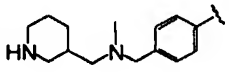
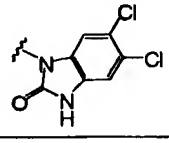
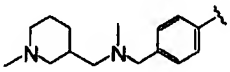
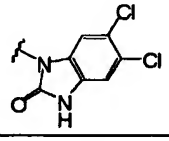
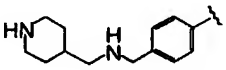
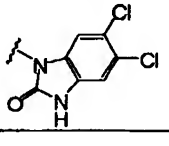
Compound Number		n	R^2	Y	R^1
291		0	H	O	
292		0	H	O	
293		0	H	O	
294		0	H	O	
295		0	H	O	
296		0	H	O	
297		0	H	O	
298		0	H	O	
299		0	H	O	
300		0	H	O	

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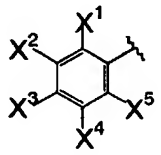
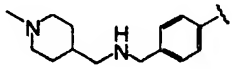
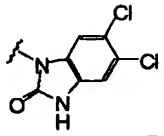
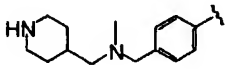
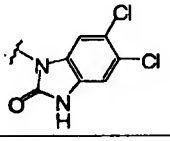
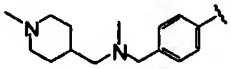
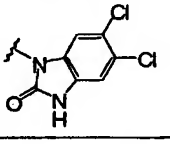
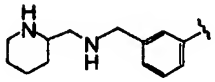
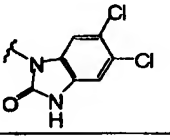
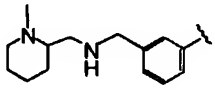
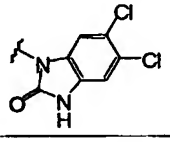
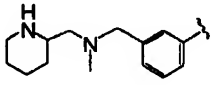
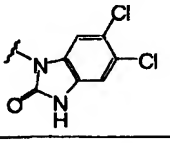
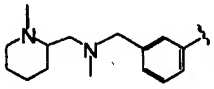
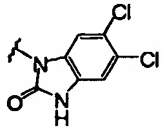
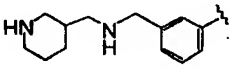
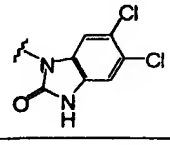
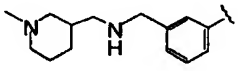
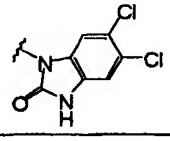
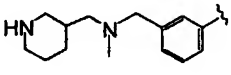
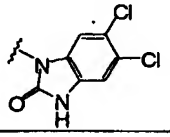
Compound Number		n	R^2	Y	R^1
301		0	H	O	
302		0	H	O	
303		0	H	O	
304		0	H	O	
305		0	H	O	
306		0	H	O	
307		0	H	O	
308		0	H	O	
309		0	H	O	
310		0	H	O	

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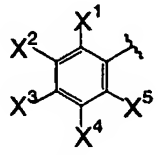
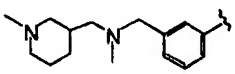
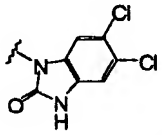
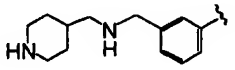
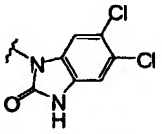
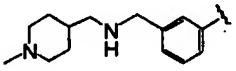
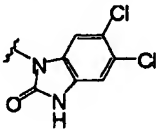
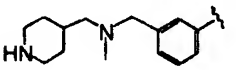
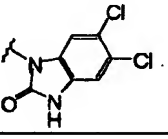
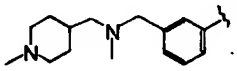
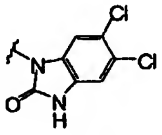
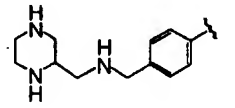
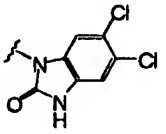
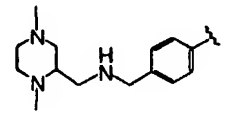
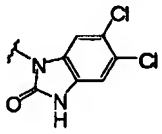
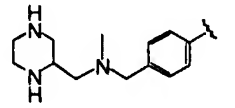
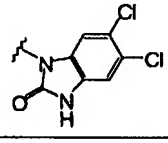
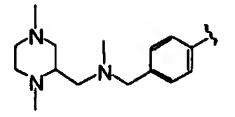
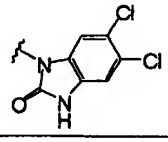
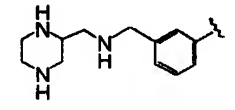
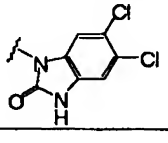
Compound Number		n	R^2	Y	R^1
311		0	H	O	
312		0	H	O	
313		0	H	O	
314		0	H	O	
315		0	H	O	
316		0	H	O	
317		0	H	O	
318		0	H	O	
319		0	H	O	
320		0	H	O	

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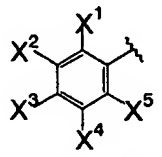
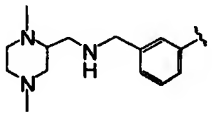
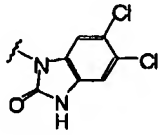
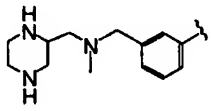
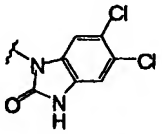
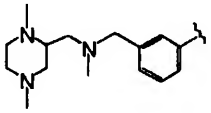
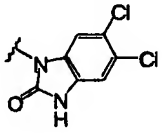
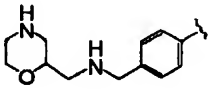
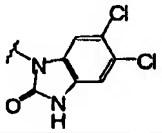
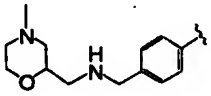
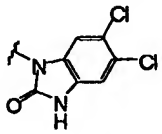
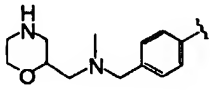
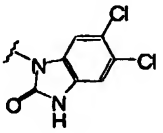
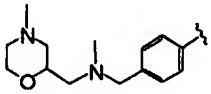
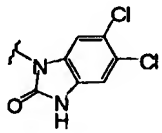
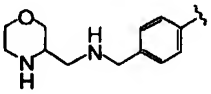
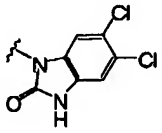
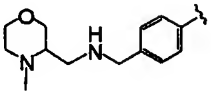
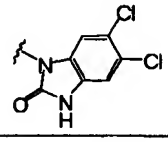
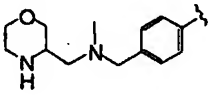
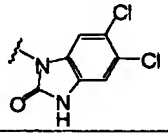
Compound Number		n	R^2	Y	R^1
321		0	H	O	
322		0	H	O	
323		0	H	O	
324		0	H	O	
325		0	H	O	
326		0	H	O	
327		0	H	O	
328		0	H	O	
329		0	H	O	
330		0	H	O	

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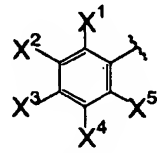
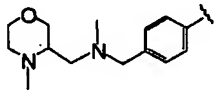
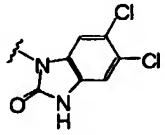
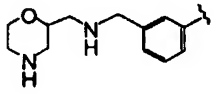
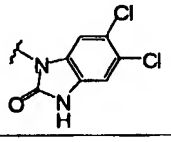
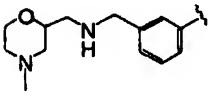
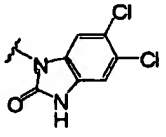
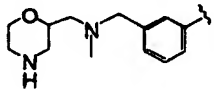
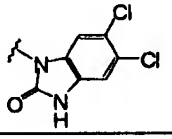
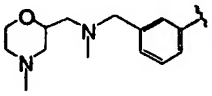
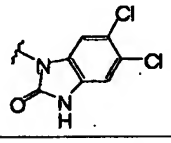
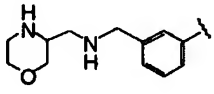
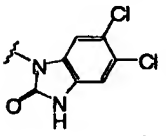
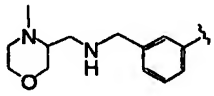
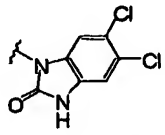
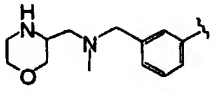
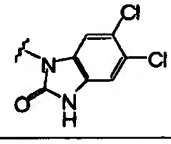
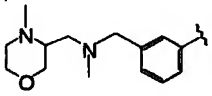
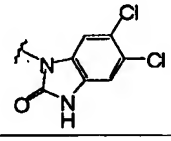
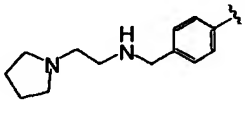
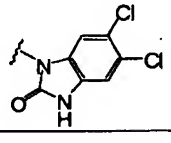
Compound Number		n	R^2	Y	R^1
331		0	H	O	
332		0	H	O	
333		0	H	O	
334		0	H	O	
335		0	H	O	
336		0	H	O	
337		0	H	O	
338		0	H	O	
339		0	H	O	
340		0	H	O	

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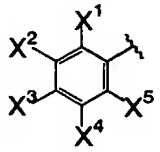
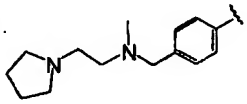
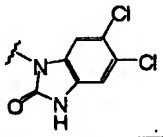
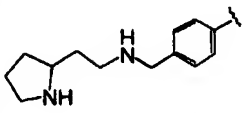
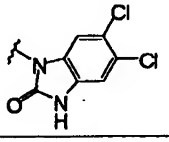
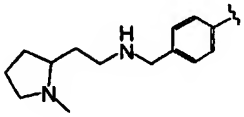
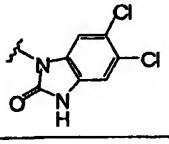
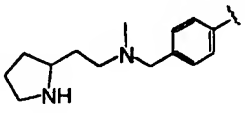
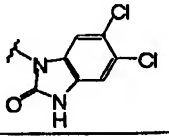
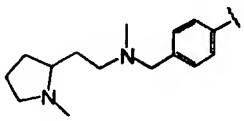
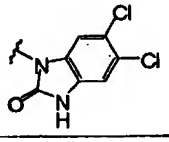
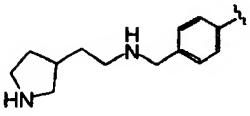
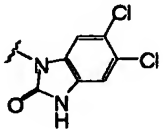
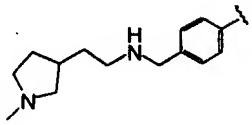
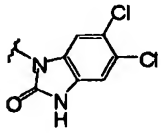
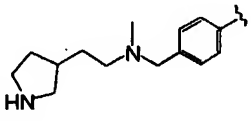
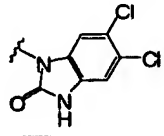
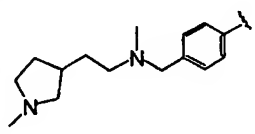
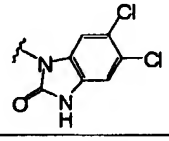
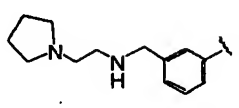
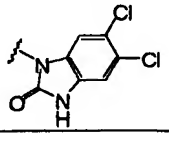
Compound Number		n	R^2	Y	R^1
341		0	H	O	
342		0	H	O	
343		0	H	O	
344		0	H	O	
345		0	H	O	
346		0	H	O	
347		0	H	O	
348		0	H	O	
349		0	H	O	
350		0	H	O	

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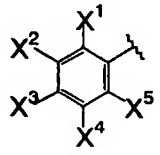
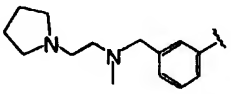
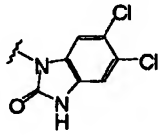
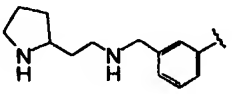
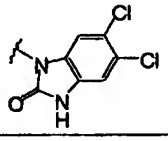
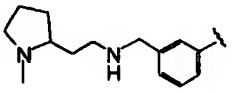
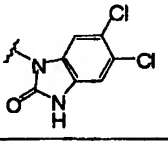
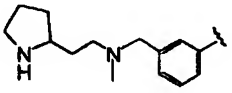
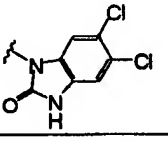
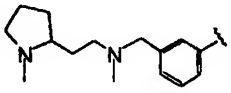
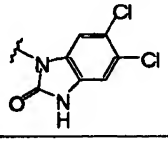
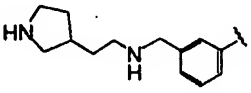
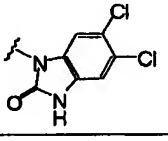
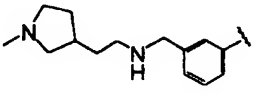
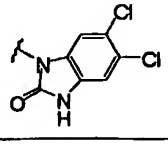
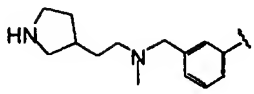
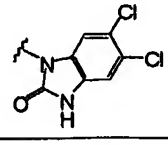
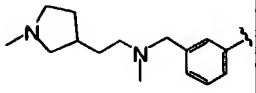
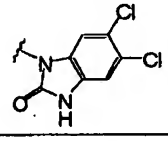
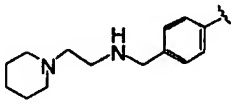
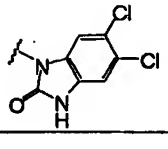
Compound Number		n	R^2	Y	R^1
351		0	H	O	
352		0	H	O	
353		0	H	O	
354		0	H	O	
355		0	H	O	
356		0	H	O	
357		0	H	O	
358		0	H	O	
359		0	H	O	
360		0	H	O	

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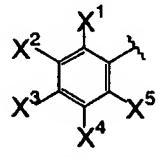
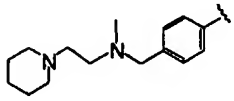
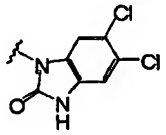
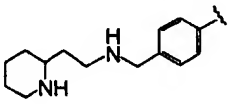
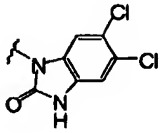
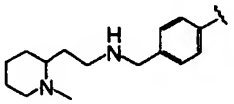
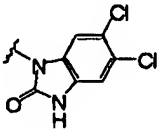
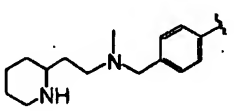
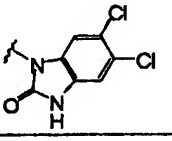
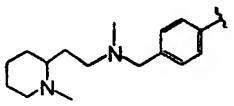
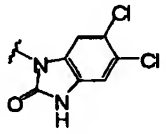
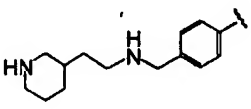
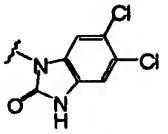
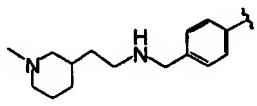
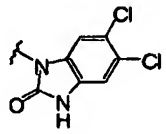
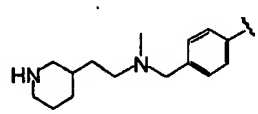
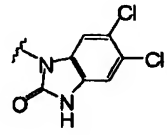
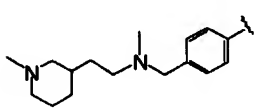
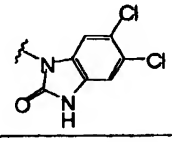
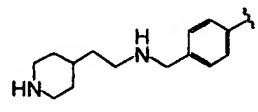
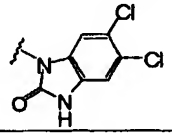
Compound Number		n	R^2	Y	R^1
361		0	H	O	
362		0	H	O	
363		0	H	O	
364		0	H	O	
365		0	H	O	
366		0	H	O	
367		0	H	O	
368		0	H	O	
369		0	H	O	
370		0	H	O	

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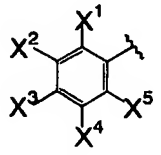
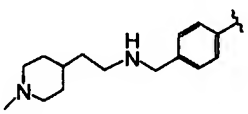
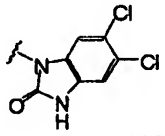
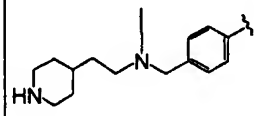
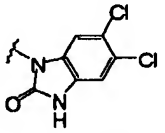
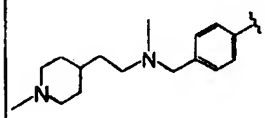
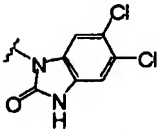
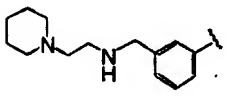
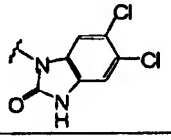
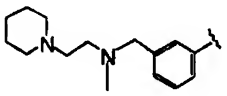
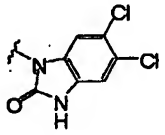
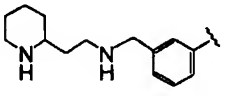
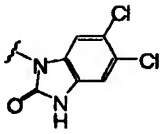
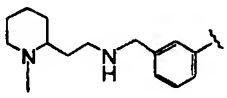
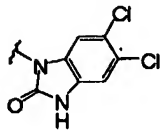
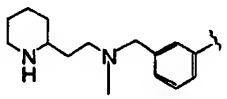
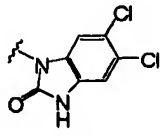
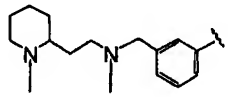
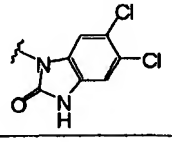
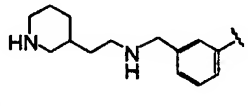
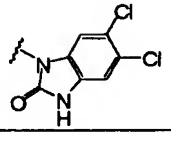
Compound Number		n	R^2	Y	R^1
371		0	H	O	
372		0	H	O	
373		0	H	O	
374		0	H	O	
375		0	H	O	
376		0	H	O	
377		0	H	O	
378		0	H	O	
379		0	H	O	
380		0	H	O	

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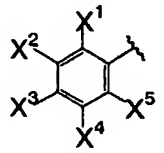
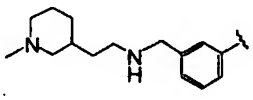
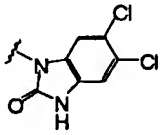
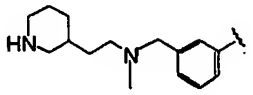
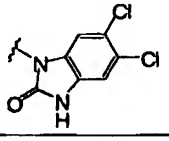
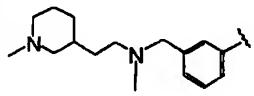
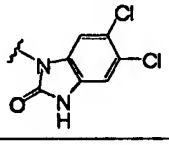
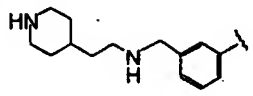
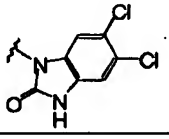
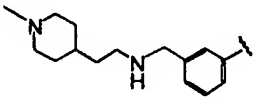
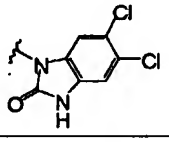
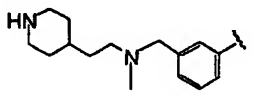
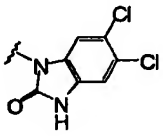
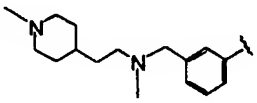
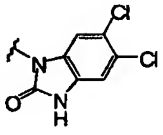
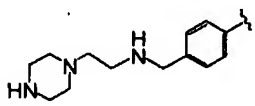
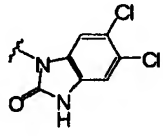
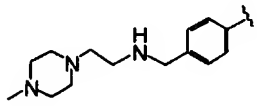
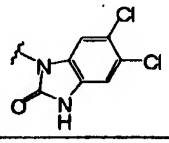
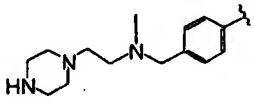
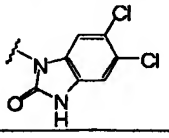
Compound Number		n	R^2	Y	R^1
381		0	H	O	
382		0	H	O	
383		0	H	O	
384		0	H	O	
385		0	H	O	
386		0	H	O	
387		0	H	O	
388		0	H	O	
389		0	H	O	
390		0	H	O	

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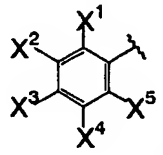
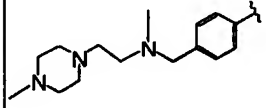
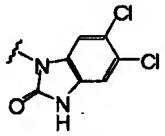
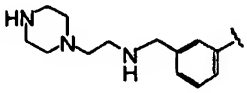
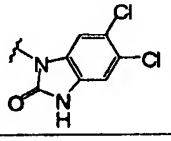
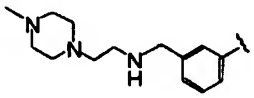
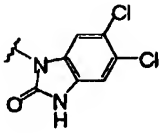
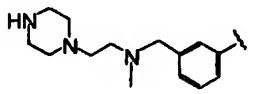
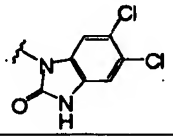
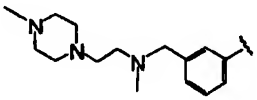
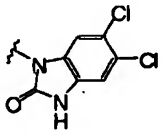
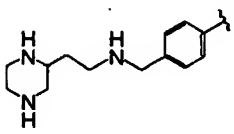
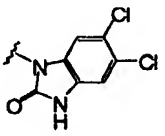
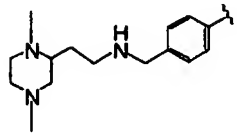
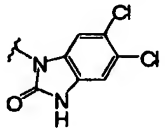
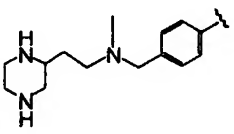
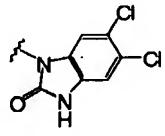
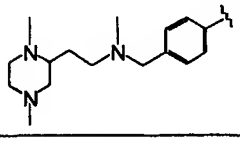
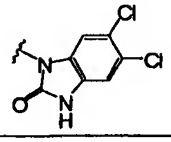
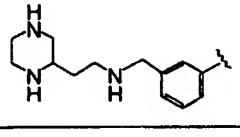
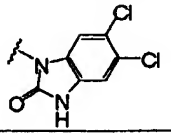
Compound Number		n	R^2	Y	R^1
391		0	H	O	
392		0	H	O	
393		0	H	O	
394		0	H	O	
395		0	H	O	
396		0	H	O	
397		0	H	O	
398		0	H	O	
399		0	H	O	
400		0	H	O	

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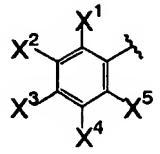
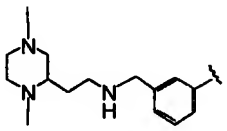
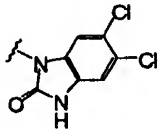
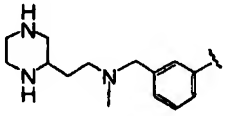
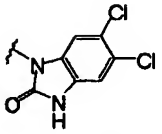
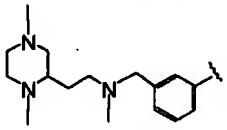
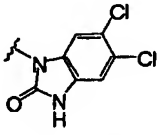
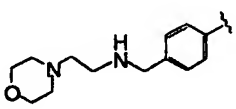
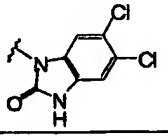
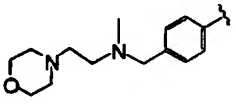
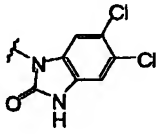
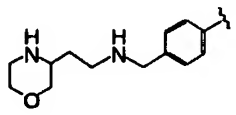
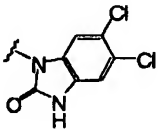
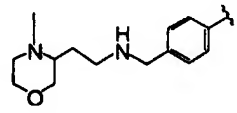
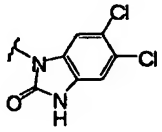
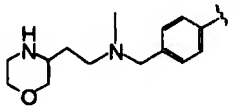
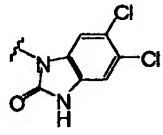
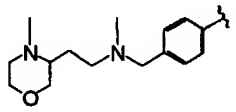
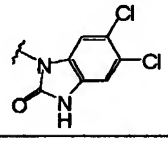
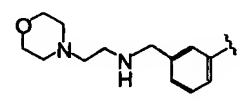
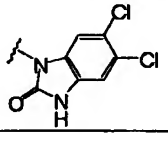
Compound Number		n	R^2	Y	R^1
401		0	H	O	
402		0	H	O	
403		0	H	O	
404		0	H	O	
405		0	H	O	
406		0	H	O	
407		0	H	O	
408		0	H	O	
409		0	H	O	
410		0	H	O	

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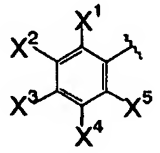
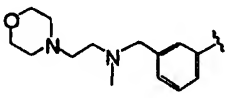
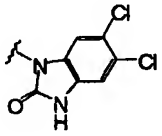
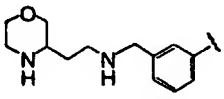
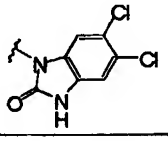
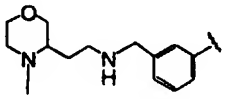
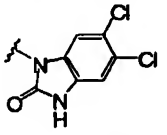
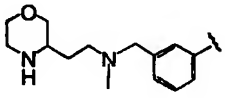
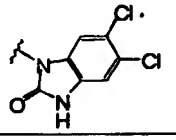
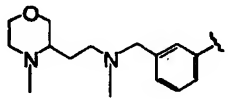
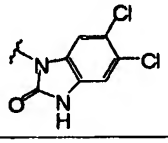
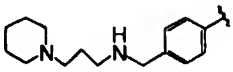
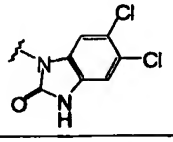
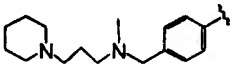
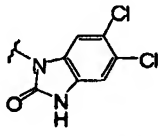
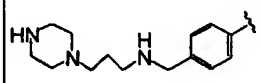
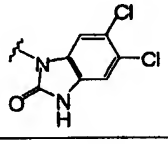
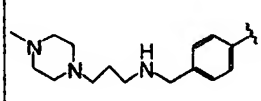
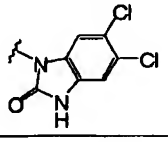
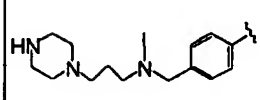
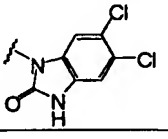
Compound Number		n	R^2	Y	R^1
411		0	H	O	
412		0	H	O	
413		0	H	O	
414		0	H	O	
415		0	H	O	
416		0	H	O	
417		0	H	O	
418		0	H	O	
419		0	H	O	
420		0	H	O	

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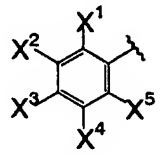
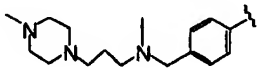
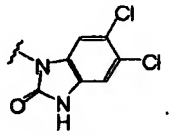
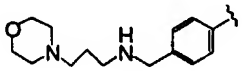
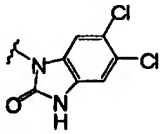
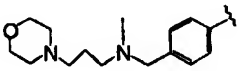
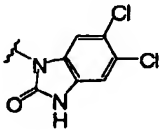
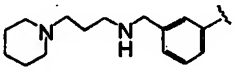
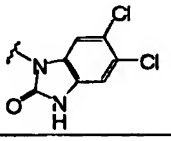
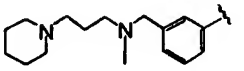
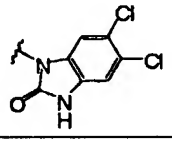
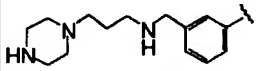
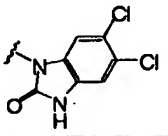
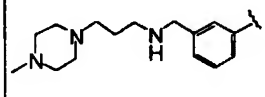
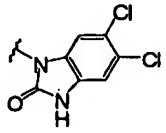
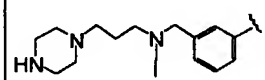
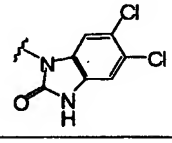
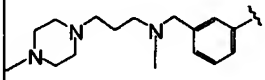
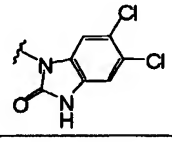
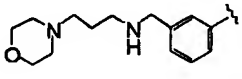
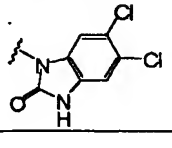
Compound Number		n	R^2	Y	R^1
421		0	H	O	
422		0	H	O	
423		0	H	O	
424		0	H	O	
425		0	H	O	
426		0	H	O	
427		0	H	O	
428		0	H	O	
429		0	H	O	
430		0	H	O	

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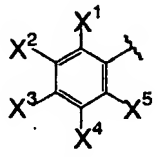
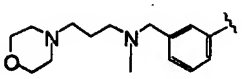
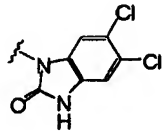
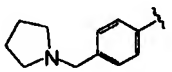
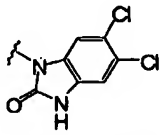
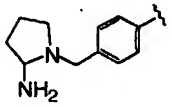
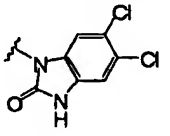
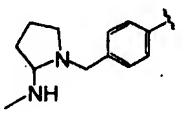
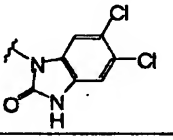
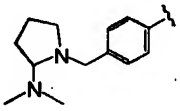
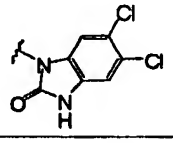
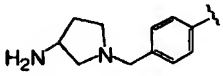
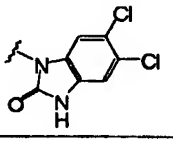
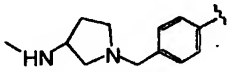
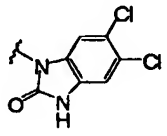
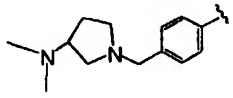
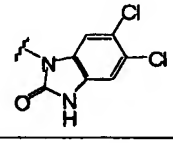
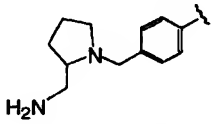
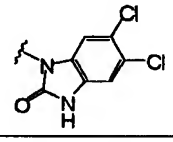
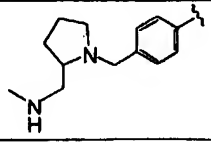
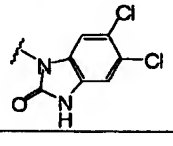
Compound Number		n	R^2	Y	R^1
431		0	H	O	
432		0	H	O	
433		0	H	O	
434		0	H	O	
435		0	H	O	
436		0	H	O	
437		0	H	O	
438		0	H	O	
439		0	H	O	
440		0	H	O	

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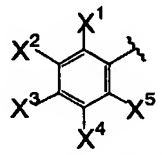
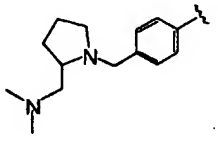
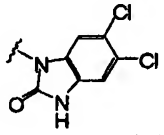
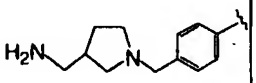
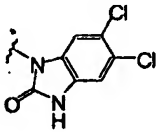
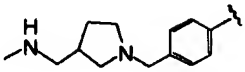
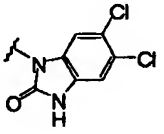
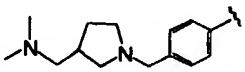
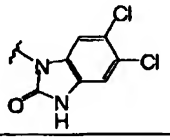
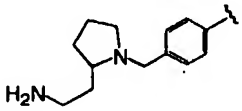
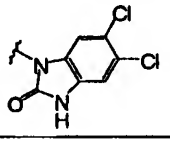
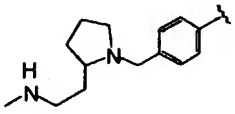
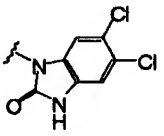
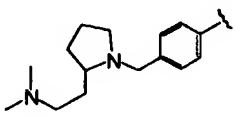
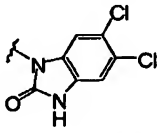
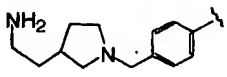
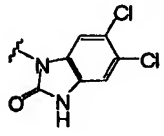
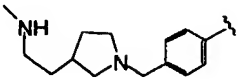
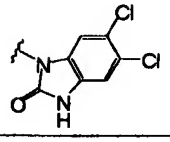
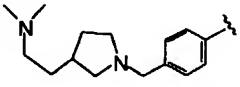
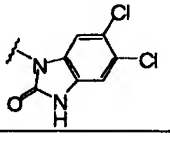
Compound Number		n	R^2	Y	R^1
441		0	H	O	
442		0	H	O	
443		0	H	O	
444		0	H	O	
445		0	H	O	
446		0	H	O	
447		0	H	O	
448		0	H	O	
449		0	H	O	
450		0	H	O	

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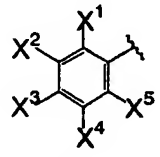
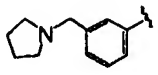
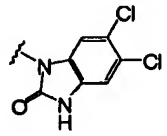
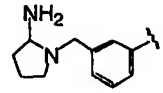
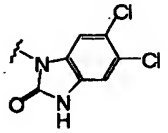
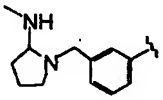
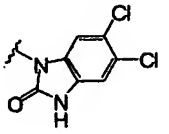
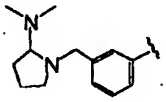
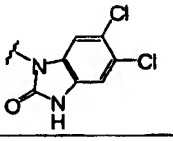
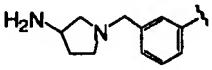
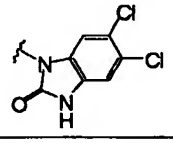
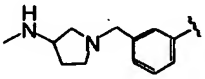
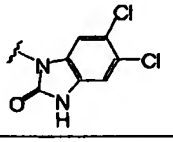
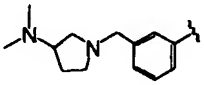
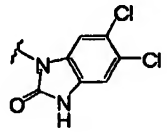
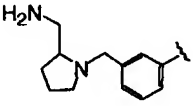
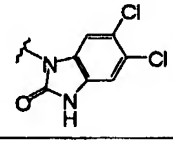
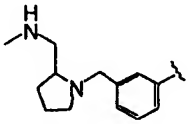
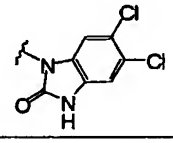
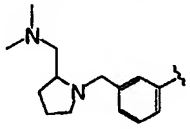
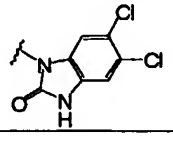
Compound Number		n	R^2	Y	R^1
451		0	H	O	
452		0	H	O	
453		0	H	O	
454		0	H	O	
455		0	H	O	
456		0	H	O	
457		0	H	O	
458		0	H	O	
459		0	H	O	
460		0	H	O	

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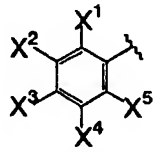
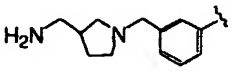
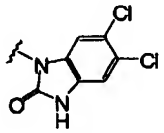
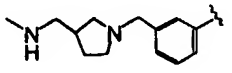
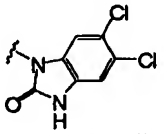
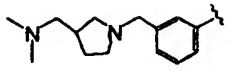
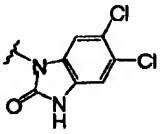
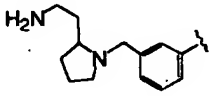
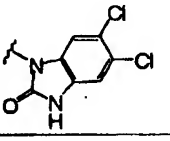
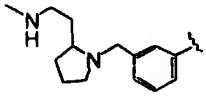
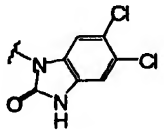
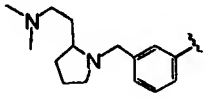
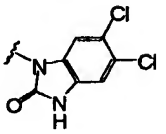
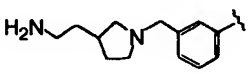
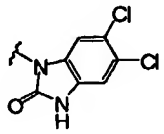
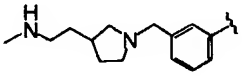
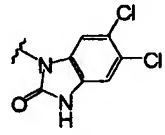
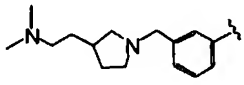
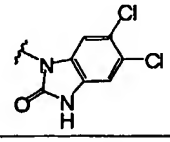
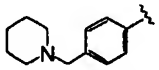
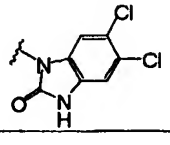
Compound Number		n	R^2	Y	R^1
461		0	H	O	
462		0	H	O	
463		0	H	O	
464		0	H	O	
465		0	H	O	
466		0	H	O	
467		0	H	O	
468		0	H	O	
469		0	H	O	
470		0	H	O	

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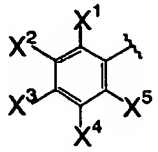
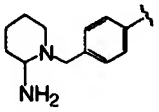
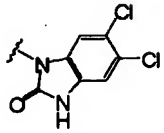
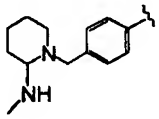
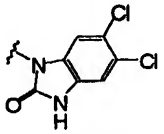
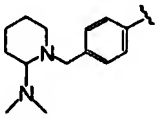
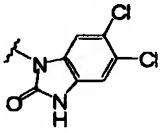
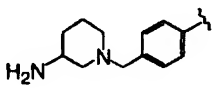
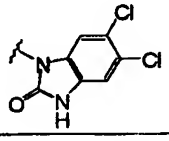
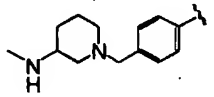
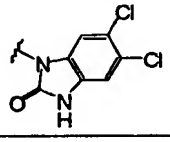
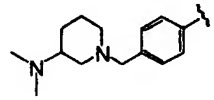
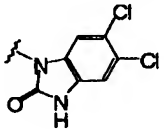
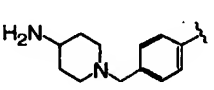
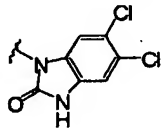
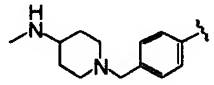
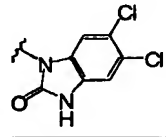
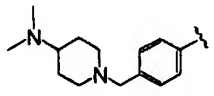
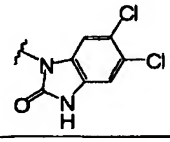
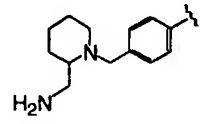
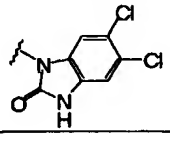
Compound Number		n	R^2	Y	R^1
471		0	H	O	
472		0	H	O	
473		0	H	O	
474		0	H	O	
475		0	H	O	
476		0	H	O	
477		0	H	O	
478		0	H	O	
479		0	H	O	
480		0	H	O	

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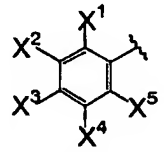
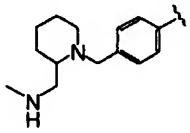
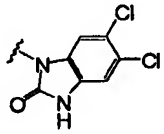
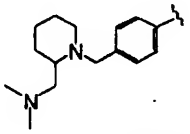
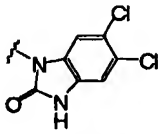
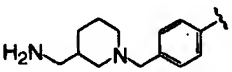
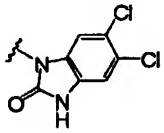
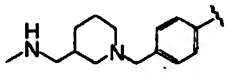
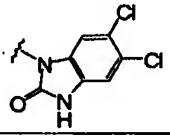
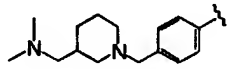
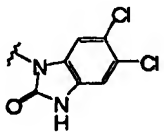
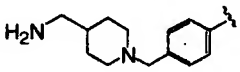
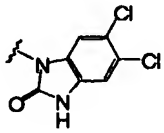
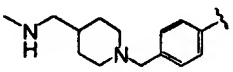
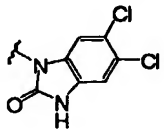
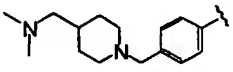
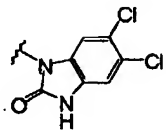
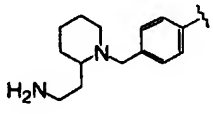
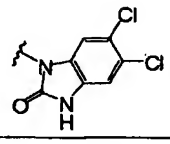
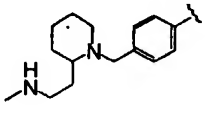
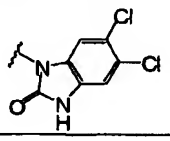
Compound Number		n	R^2	Y	R^1
481		0	H	O	
482		0	H	O	
483		0	H	O	
484		0	H	O	
485		0	H	O	
486		0	H	O	
487		0	H	O	
488		0	H	O	
489		0	H	O	
490		0	H	O	

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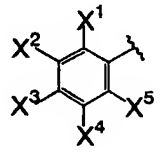
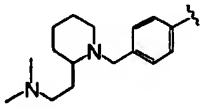
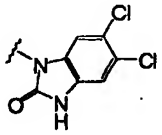
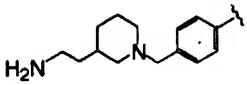
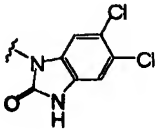
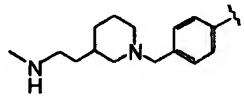
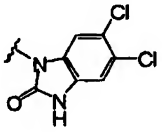
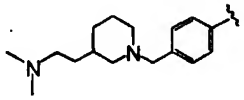
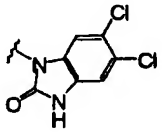
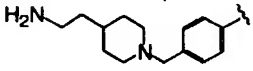
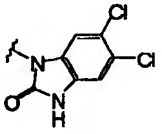
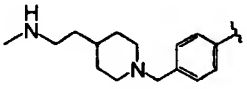
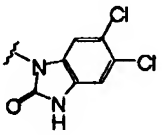
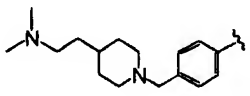
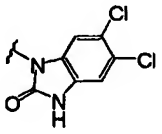
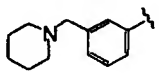
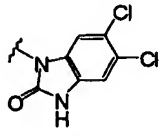
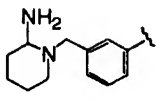
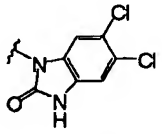
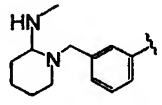
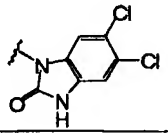
Compound Number		n	R^2	Y	R^1
491		0	H	O	
492		0	H	O	
493		0	H	O	
494		0	H	O	
495		0	H	O	
496		0	H	O	
497		0	H	O	
498		0	H	O	
499		0	H	O	
500		0	H	O	

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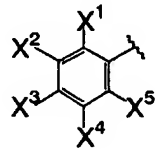
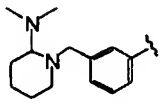
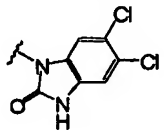
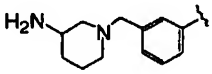
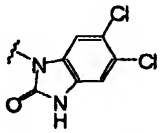
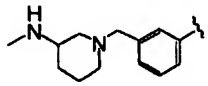
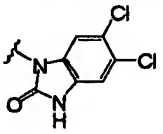
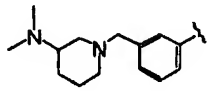
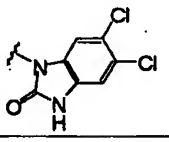
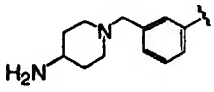
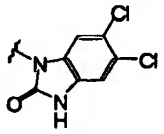
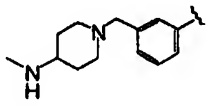
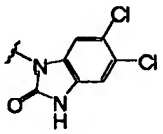
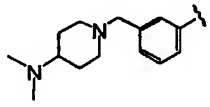
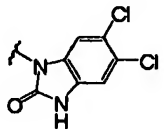
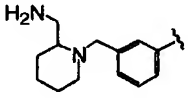
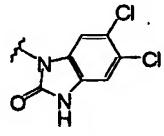
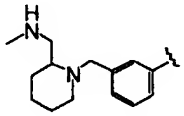
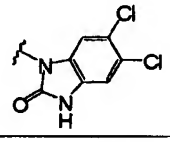
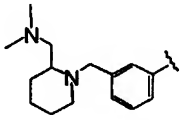
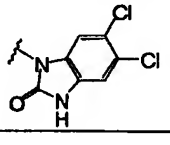
Compound Number		n	R^2	Y	R^1
501		0	H	O	
502		0	H	O	
503		0	H	O	
504		0	H	O	
505		0	H	O	
506		0	H	O	
507		0	H	O	
508		0	H	O	
509		0	H	O	
510		0	H	O	

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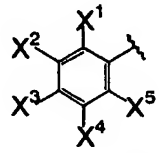
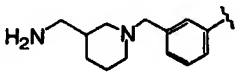
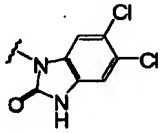
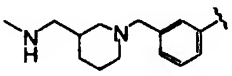
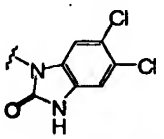
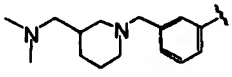
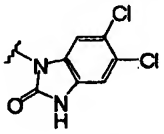
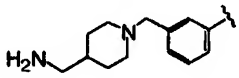
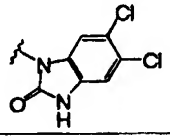
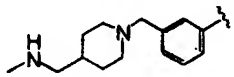
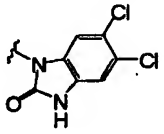
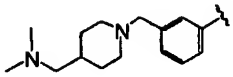
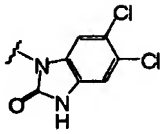
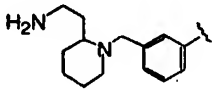
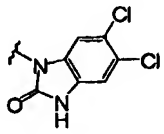
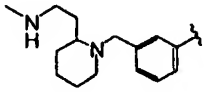
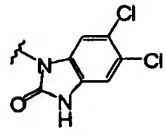
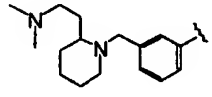
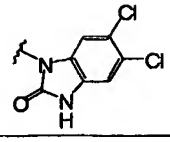
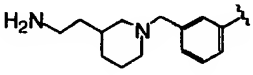
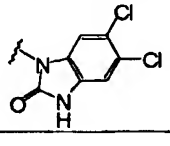
Compound Number		n	R^2	Y	R^1
511		0	H	O	
512		0	H	O	
513		0	H	O	
514		0	H	O	
515		0	H	O	
516		0	H	O	
517		0	H	O	
518		0	H	O	
519		0	H	O	
520		0	H	O	

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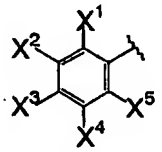
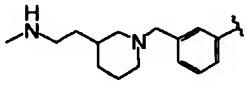
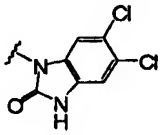
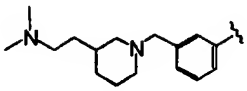
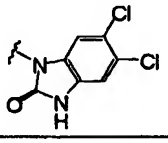
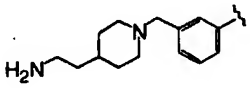
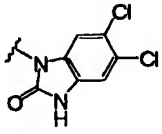
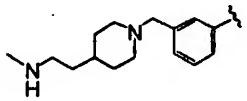
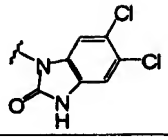
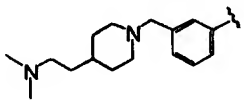
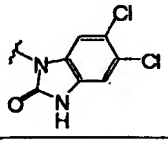
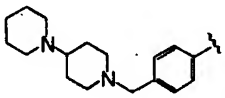
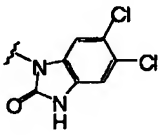
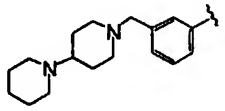
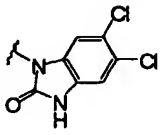
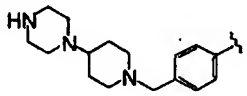
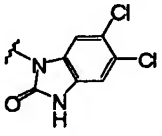
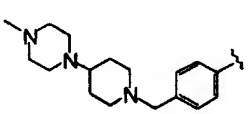
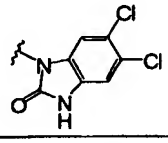
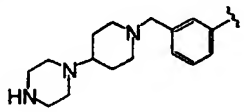
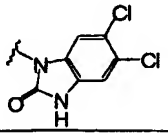
Compound Number		n	R^2	Y	R^1
521		0	H	O	
522		0	H	O	
523		0	H	O	
524		0	H	O	
525		0	H	O	
526		0	H	O	
527		0	H	O	
528		0	H	O	
529		0	H	O	
530		0	H	O	

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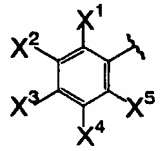
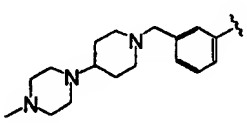
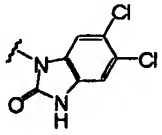
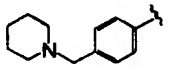
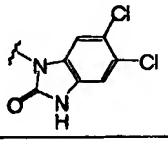
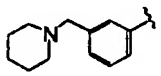
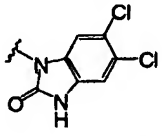
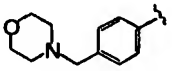
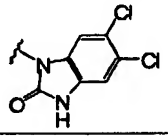
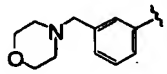
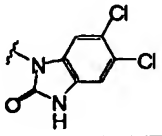
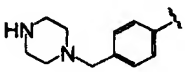
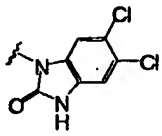
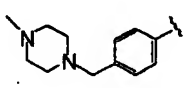
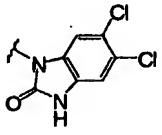
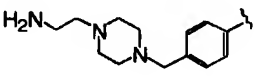
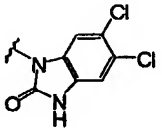
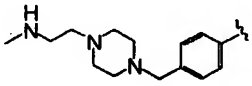
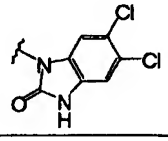
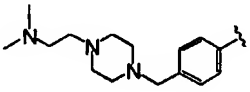
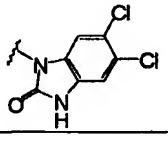
Compound Number		n	R^2	Y	R^1
531		0	H	O	
532		0	H	S	
533		0	H	S	
534		0	H	O	
535		0	H	O	
536		0	H	O	
537		0	H	O	
538		0	H	O	
539		0	H	O	
540		0	H	O	

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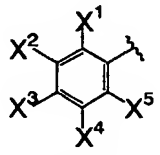
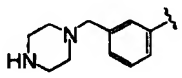
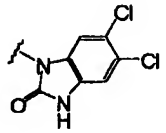
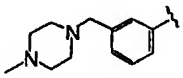
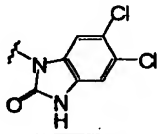
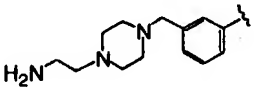
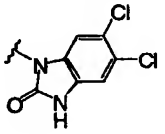
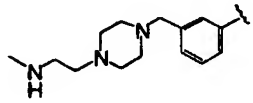
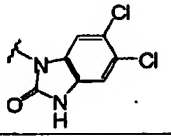
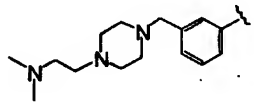
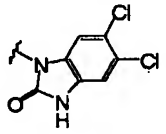
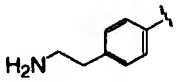
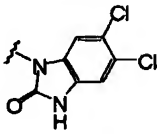
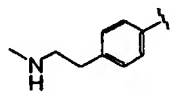
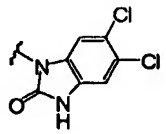
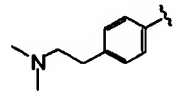
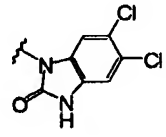
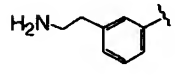
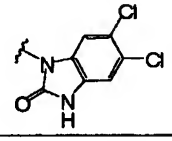
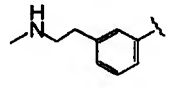
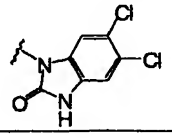
Compound Number		n	R^2	Y	R^1
541		0	H	O	
542		0	H	O	
543		0	H	O	
544		0	H	O	
545		0	H	O	
546		0	H	O	
547		0	H	O	
548		0	H	O	
549		0	H	O	
550		0	H	O	

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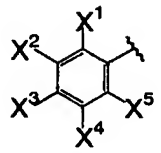
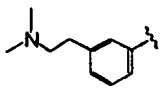
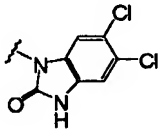
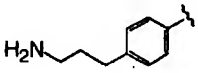
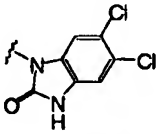
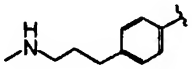
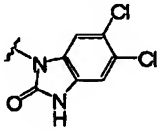
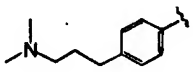
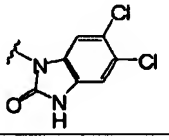
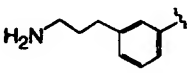
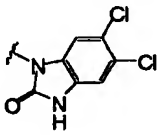
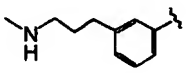
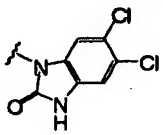
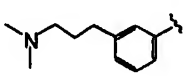
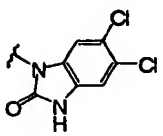
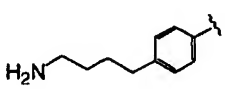
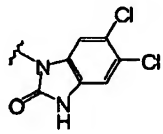
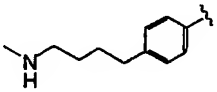
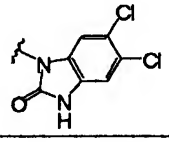
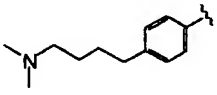
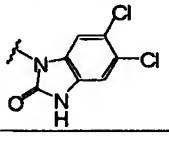
Compound Number		n	R^2	Y	R^1
551		0	H	O	
552		0	H	O	
553		0	H	O	
554		0	H	O	
555		0	H	O	
556		0	H	O	
557		0	H	O	
558		0	H	O	
559		0	H	O	
560		0	H	O	

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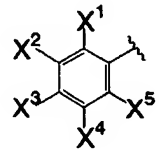
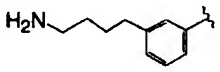
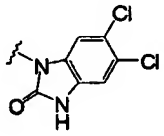
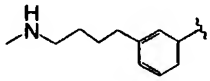
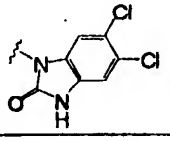
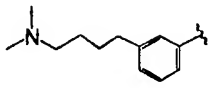
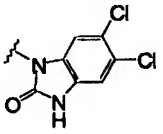
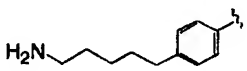
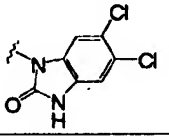
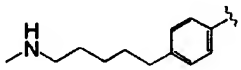
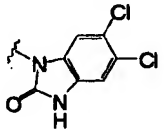
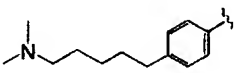
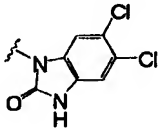
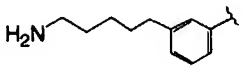
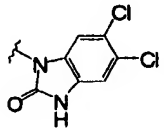
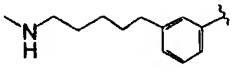
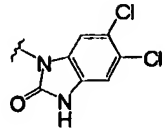
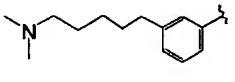
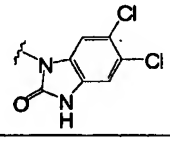
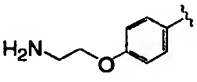
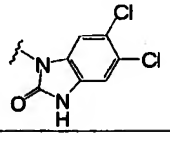
Compound Number		n	R^2	Y	R^1
561		0	H	O	
562		0	H	O	
563		0	H	O	
564		0	H	O	
565		0	H	O	
566		0	H	O	
567		0	H	O	
568		0	H	O	
569		0	H	O	
570		0	H	O	

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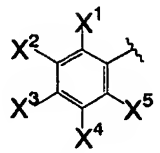
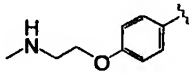
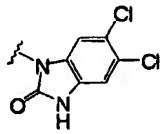
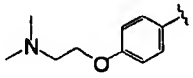
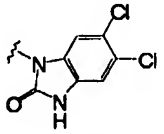
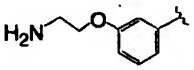
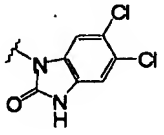
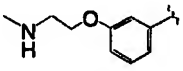
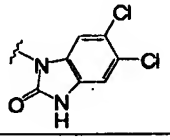
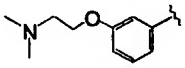
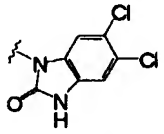
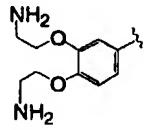
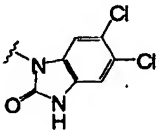
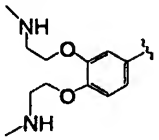
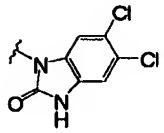
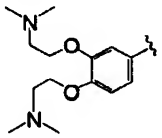
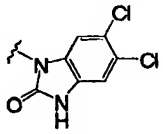
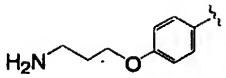
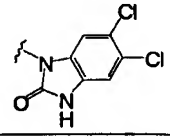
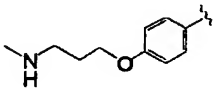
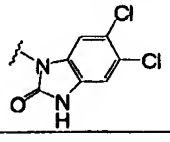
Compound Number		n	R^2	Y	R^1
571		0	H	O	
572		0	H	O	
573		0	H	O	
574		0	H	O	
575		0	H	O	
576		0	H	O	
577		0	H	O	
578		0	H	O	
579		0	H	O	
580		0	H	O	

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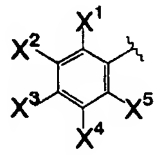
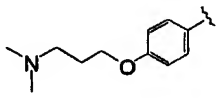
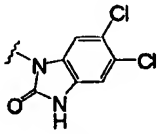
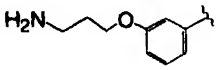
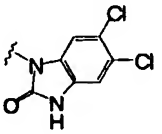
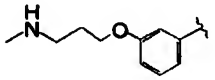
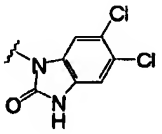
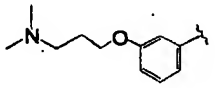
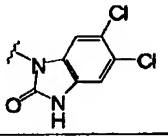
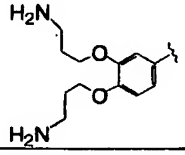
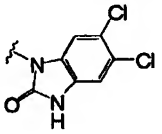
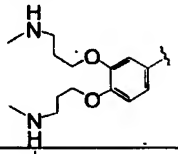
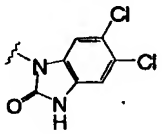
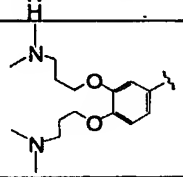
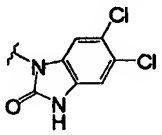
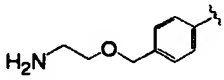
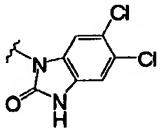
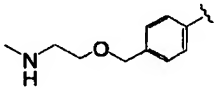
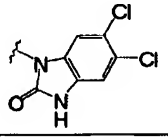
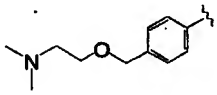
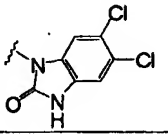
Compound Number		n	R^2	Y	R^1
581		0	H	O	
582		0	H	O	
583		0	H	O	
584		0	H	O	
585		0	H	O	
586		0	H	O	
587		0	H	O	
588		0	H	O	
589		0	H	O	
590		0	H	O	

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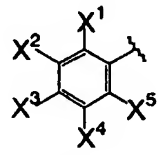
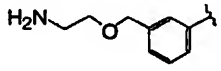
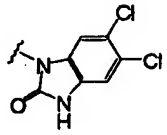
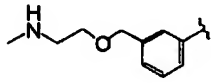
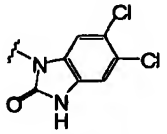
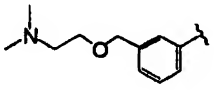
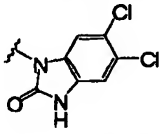
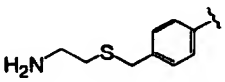
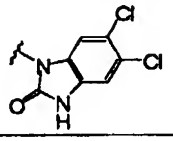
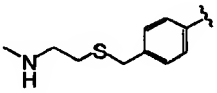
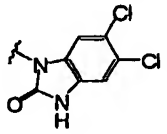
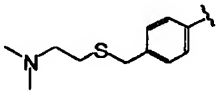
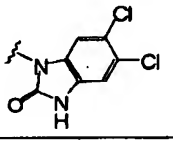
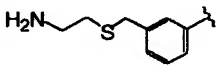
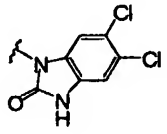
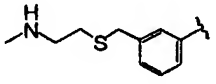
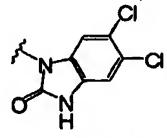
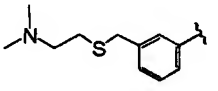
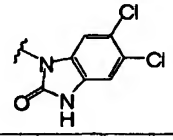
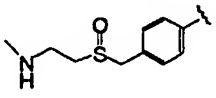
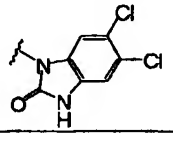
Compound Number		n	R^2	Y	R^1
591		0	H	O	
592		0	H	O	
593		0	H	O	
594		0	H	O	
595		0	H	O	
596		0	H	O	
597		0	H	O	
598		0	H	O	
599		0	H	O	
600		0	H	O	

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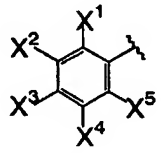
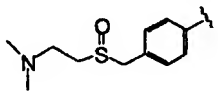
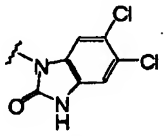
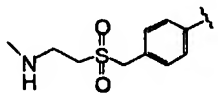
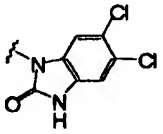
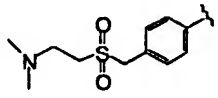
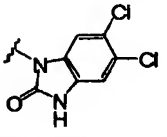
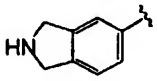
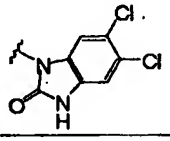
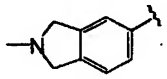
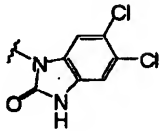
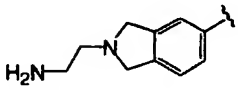
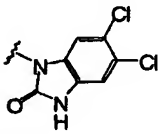
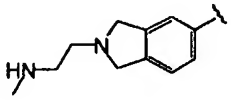
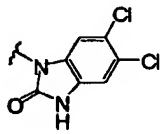
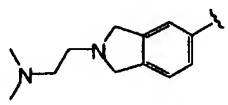
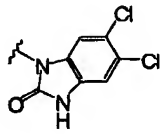
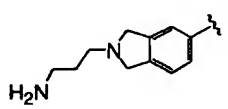
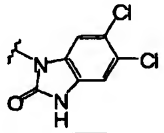
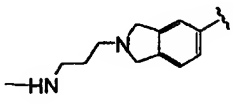
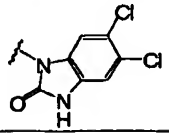
Compound Number		n	R^2	Y	R^1
601		0	H	O	
602		0	H	O	
603		0	H	O	
604		0	H	O	
605		0	H	O	
606		0	H	O	
607		0	H	O	
608		0	H	O	
609		0	H	O	
610		0	H	O	

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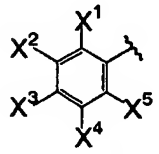
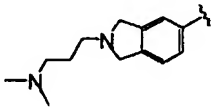
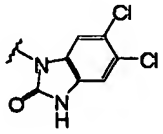
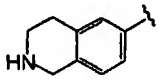
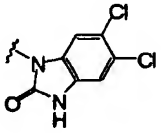
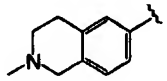
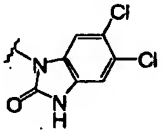
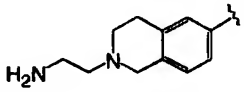
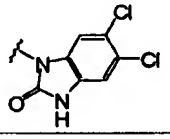
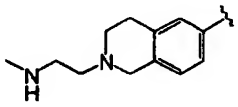
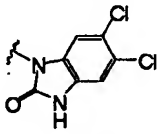
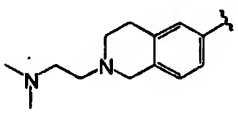
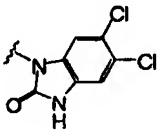
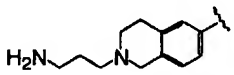
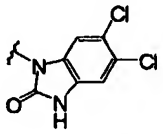
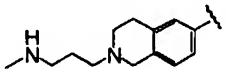
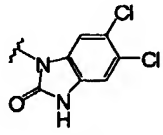
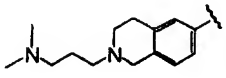
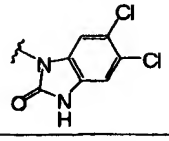
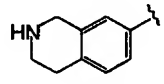
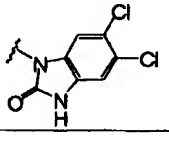
Compound Number		n	R^2	Y	R^1
611		0	H	O	
612		0	H	O	
613		0	H	O	
614		0	H	O	
615		0	H	O	
616		0	H	O	
617		0	H	O	
618		0	H	O	
619		0	H	O	
620		0	H	O	

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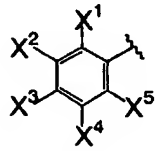
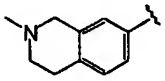
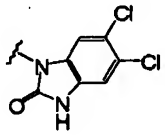
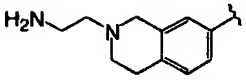
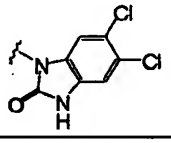
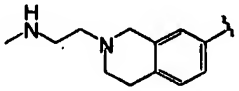
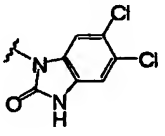
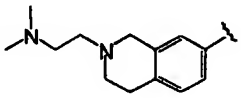
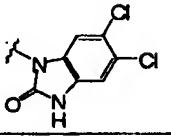
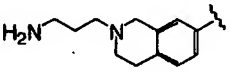
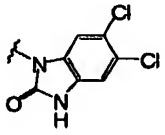
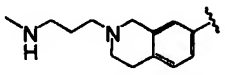
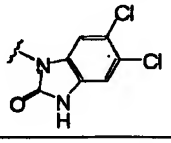
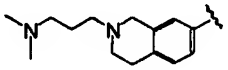
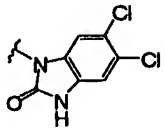
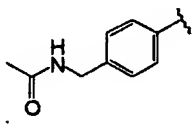
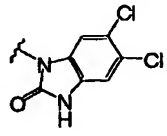
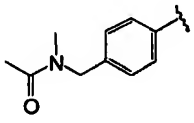
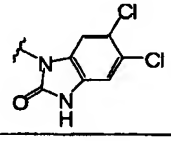
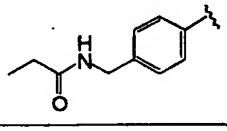
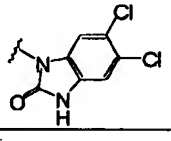
Compound Number		n	R^2	Y	R^1
621		0	H	O	
622		0	H	O	
623		0	H	O	
624		0	H	O	
625		0	H	O	
626		0	H	O	
627		0	H	O	
628		0	H	O	
629		0	H	O	
630		0	H	O	

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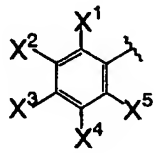
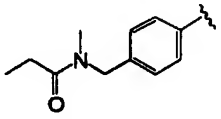
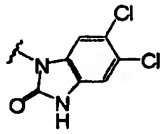
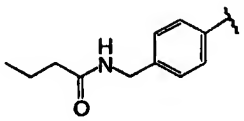
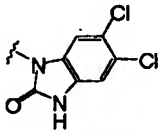
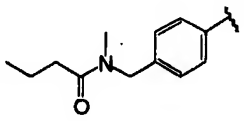
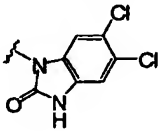
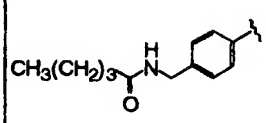
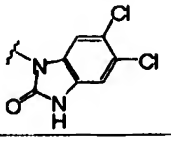
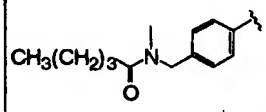
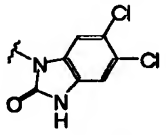
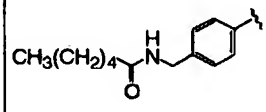
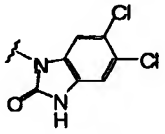
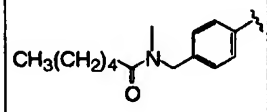
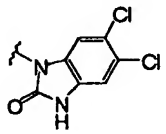
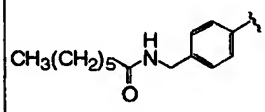
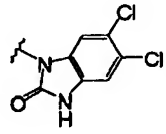
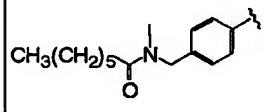
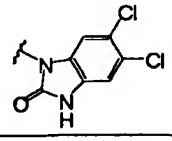
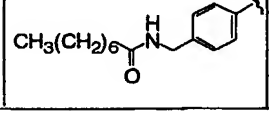
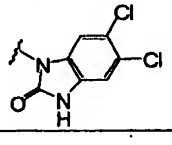
Compound Number		n	R^2	Y	R^1
631		0	H	O	
632		0	H	O	
633		0	H	O	
634		0	H	O	
635		0	H	O	
636		0	H	O	
637		0	H	O	
638		0	H	O	
639		0	H	O	
640		0	H	O	

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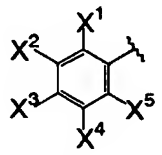
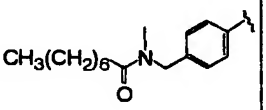
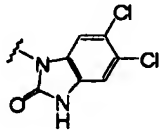
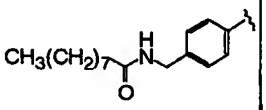
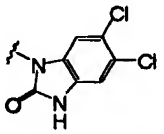
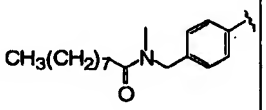
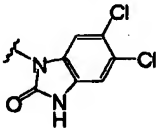
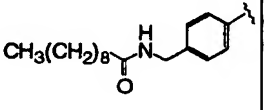
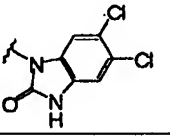
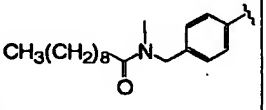
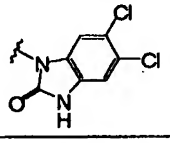
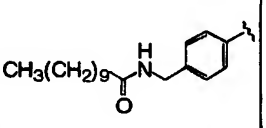
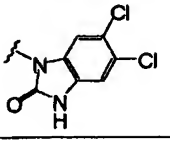
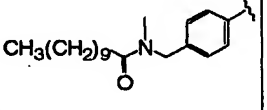
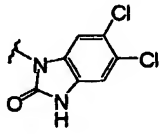
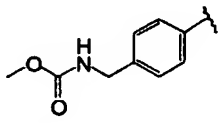
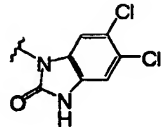
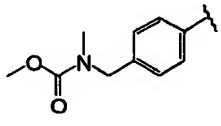
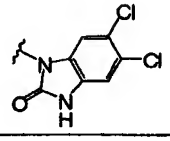
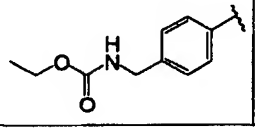
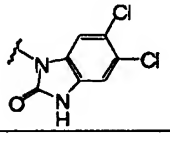
Compound Number		n	R^2	Y	R^1
641		0	H	O	
642		0	H	O	
643		0	H	O	
644		0	H	O	
645		0	H	O	
646		0	H	O	
647		0	H	O	
648		0	H	O	
649		0	H	O	
650		0	H	O	

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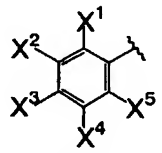
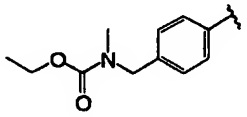
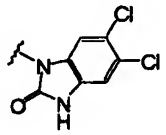
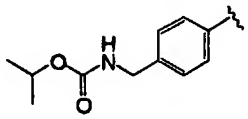
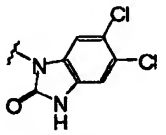
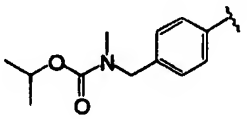
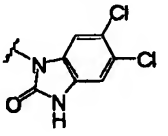
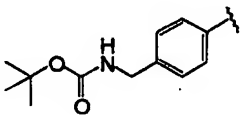
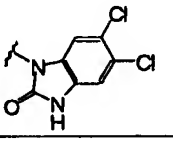
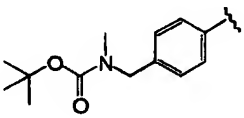
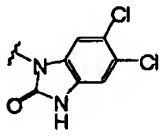
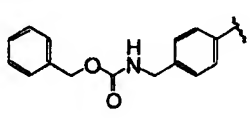
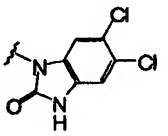
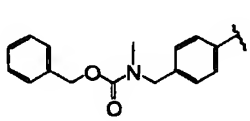
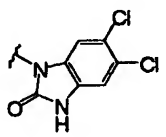
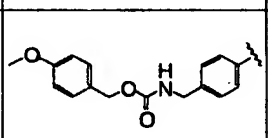
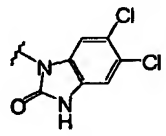
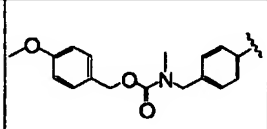
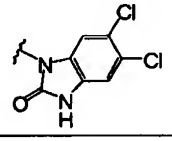
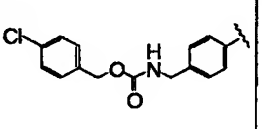
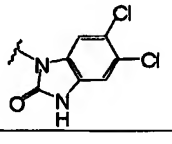
Compound Number		n	R^2	Y	R^1
651		0	H	O	
652		0	H	O	
653		0	H	O	
654		0	H	O	
655		0	H	O	
656		0	H	O	
657		0	H	O	
658		0	H	O	
659		0	H	O	
660		0	H	O	

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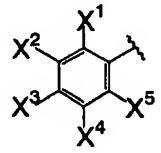
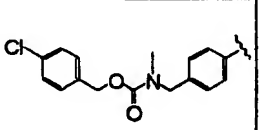
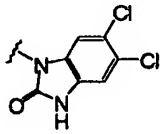
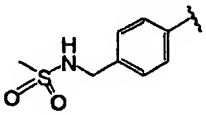
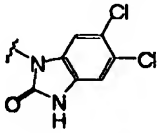
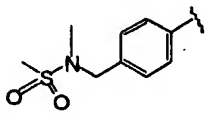
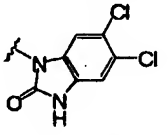
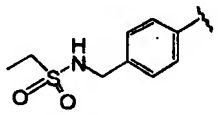
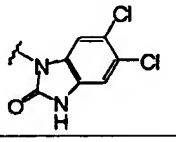
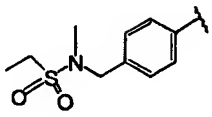
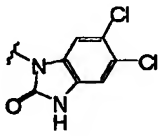
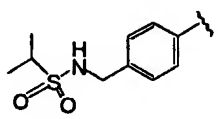
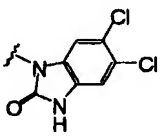
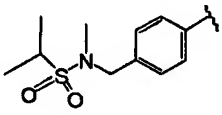
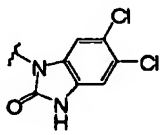
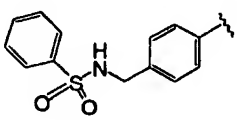
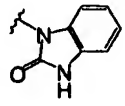
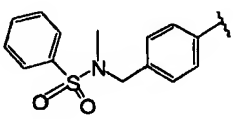
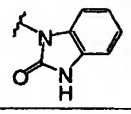
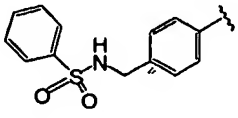
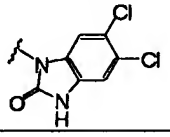
Compound Number		n	R^2	Y	R^1
661		0	H	O	
662		0	H	O	
663		0	H	O	
664		0	H	O	
665		0	H	O	
666		0	H	O	
667		0	H	O	
668		0	H	O	
669		0	H	O	
670		0	H	O	

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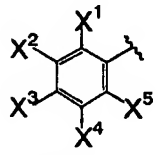
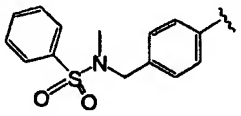
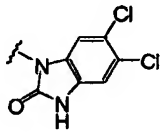
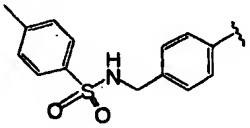
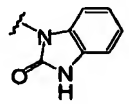
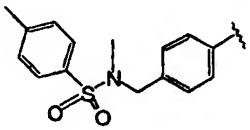
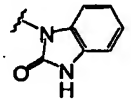
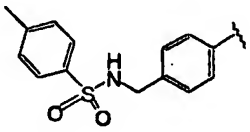
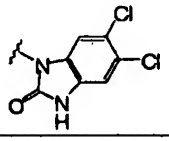
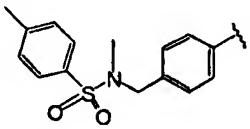
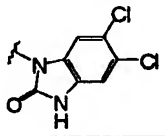
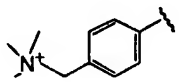
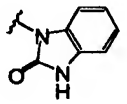
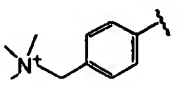
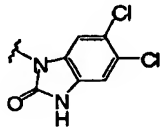
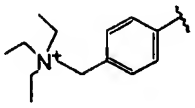
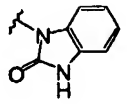
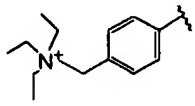
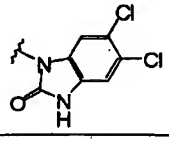
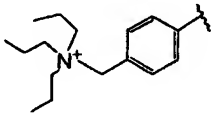
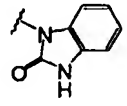
Compound Number		n	R^2	Y	R^1
671		0	H	O	
672		0	H	O	
673		0	H	O	
674		0	H	O	
675		0	H	O	
676		0	H	O	
677		0	H	O	
678		0	H	O	
679		0	H	O	
680		0	H	O	

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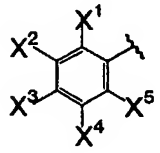
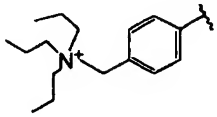
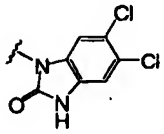
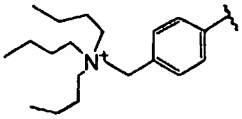
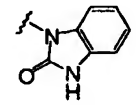
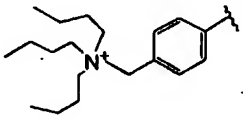
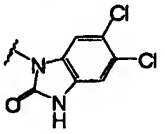
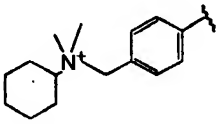
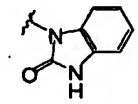
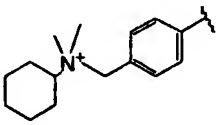
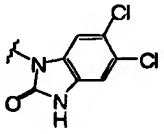
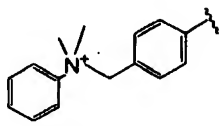
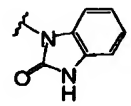
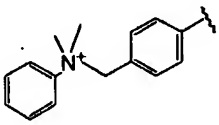
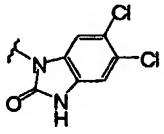
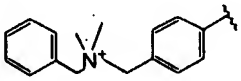
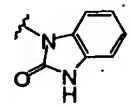
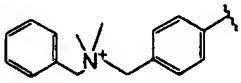
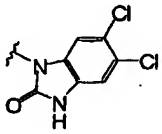
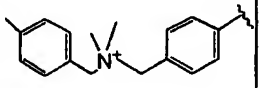
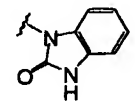
Compound Number		n	R^2	Y	R^1
681		0	H	O	
682		0	H	O	
683		0	H	O	
684		0	H	O	
685		0	H	O	
686		0	H	O	
687		0	H	O	
688		0	H	O	
689		0	H	O	
690		0	H	O	

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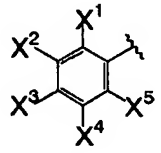
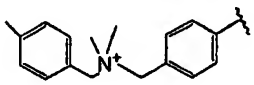
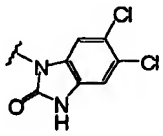
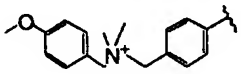
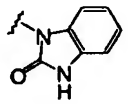
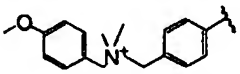
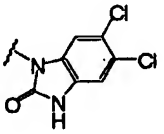
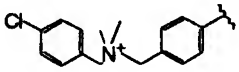
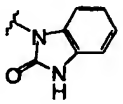
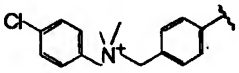
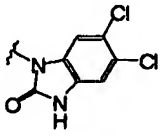
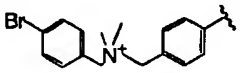
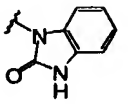
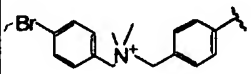
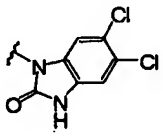
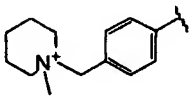
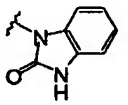
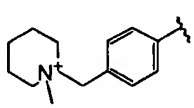
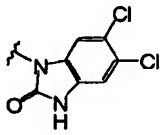
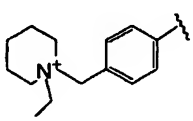
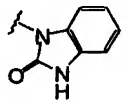
Compound Number		n	R^2	Y	R^1
691		0	H	O	
692		0	H	O	
693		0	H	O	
694		0	H	O	
695		0	H	O	
696		0	H	O	
697		0	H	O	
698		0	H	O	
699		0	H	O	
700		0	H	O	

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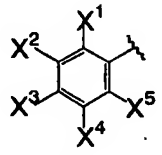
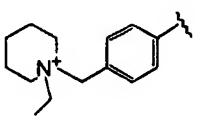
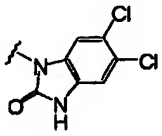
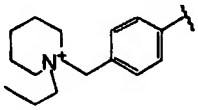
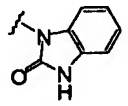
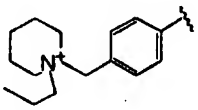
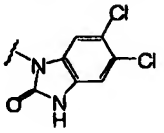
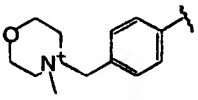
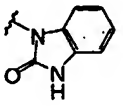
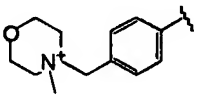
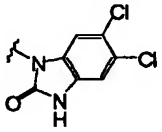
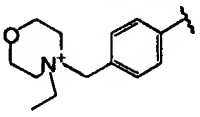
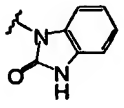
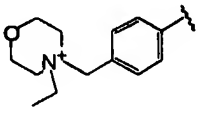
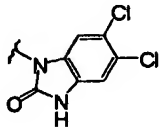
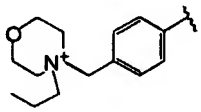
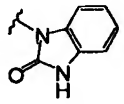
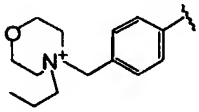
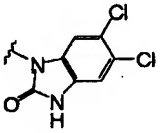
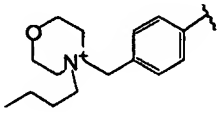
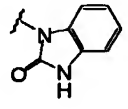
Compound Number		n	R^2	Y	R^1
701		0	H	O	
702		0	H	O	
703		0	H	O	
704		0	H	O	
705		0	H	O	
706		0	H	O	
707		0	H	O	
708		0	H	O	
709		0	H	O	
710		0	H	O	

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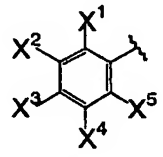
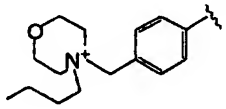
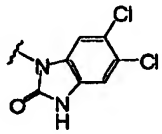
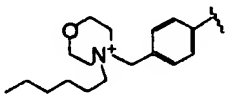
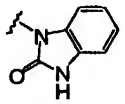
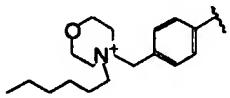
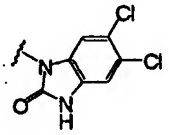
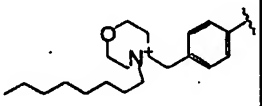
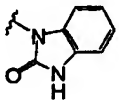
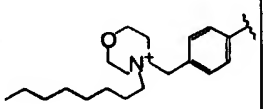
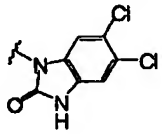
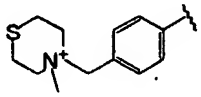
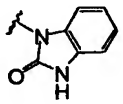
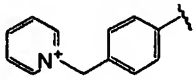
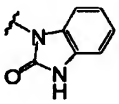
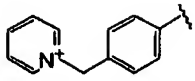
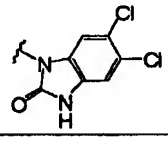
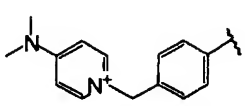
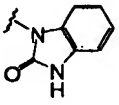
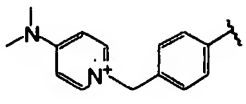
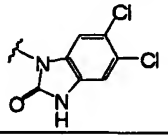
Compound Number		n	R^2	Y	R^1
711		0	H	O	
712		0	H	O	
713		0	H	O	
714		0	H	O	
715		0	H	O	
716		0	H	O	
717		0	H	O	
718		0	H	O	
719		0	H	O	
720		0	H	O	

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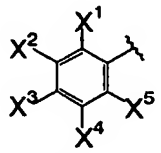
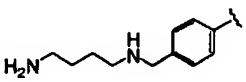
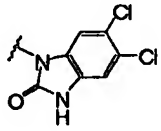
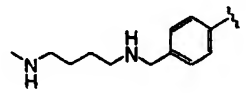
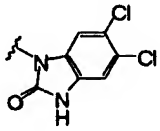
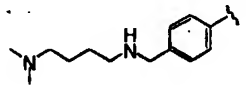
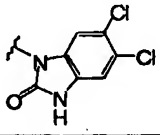
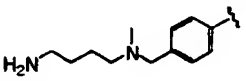
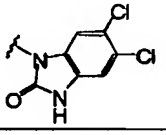
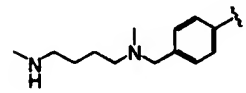
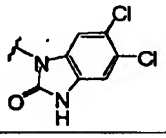
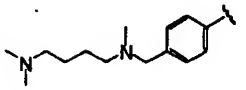
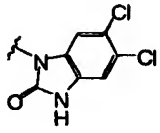
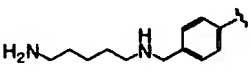
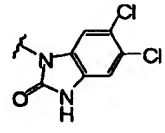
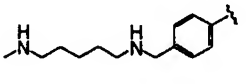
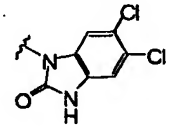
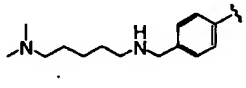
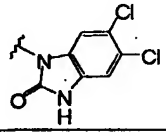
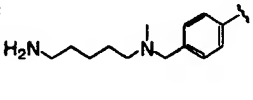
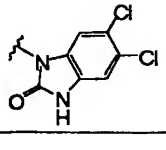
Compound Number		n	R^2	Y	R^1
721		0	H	O	
722		0	H	O	
723		0	H	O	
724		0	H	O	
725		0	H	O	
726		0	H	O	
727		0	H	O	
728		0	H	O	
729		0	H	O	
730		0	H	O	

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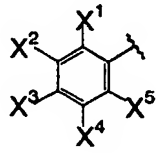
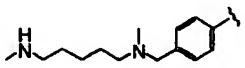
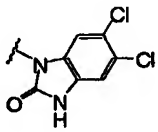
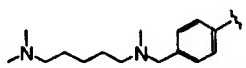
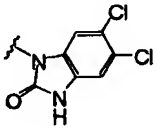
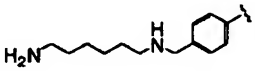
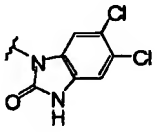
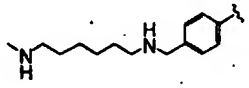
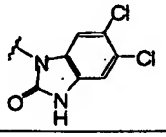
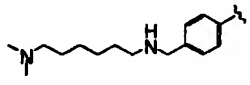
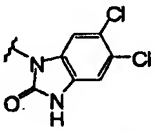
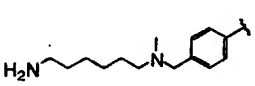
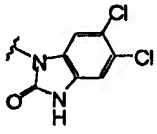
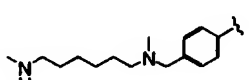
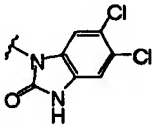
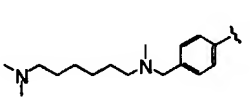
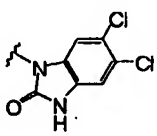
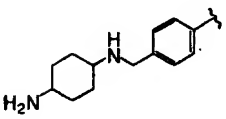
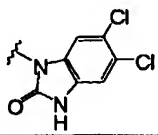
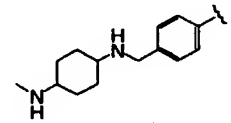
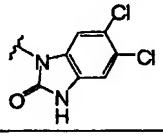
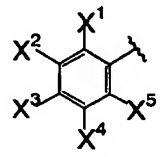
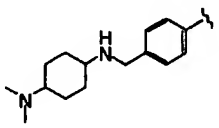
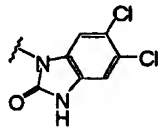
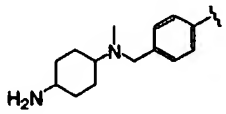
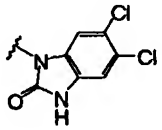
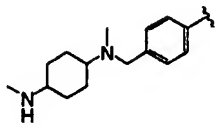
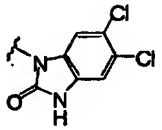
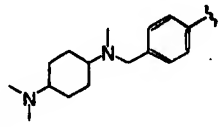
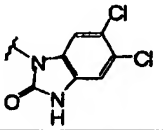
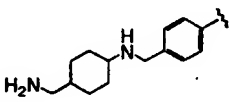
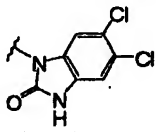
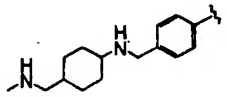
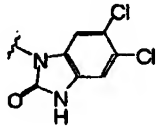
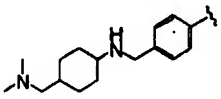
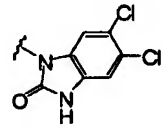
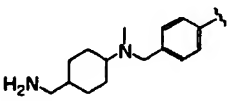
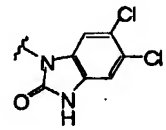
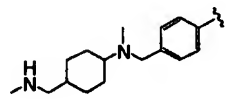
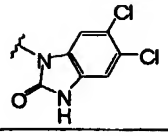
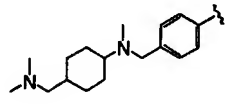
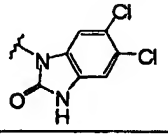
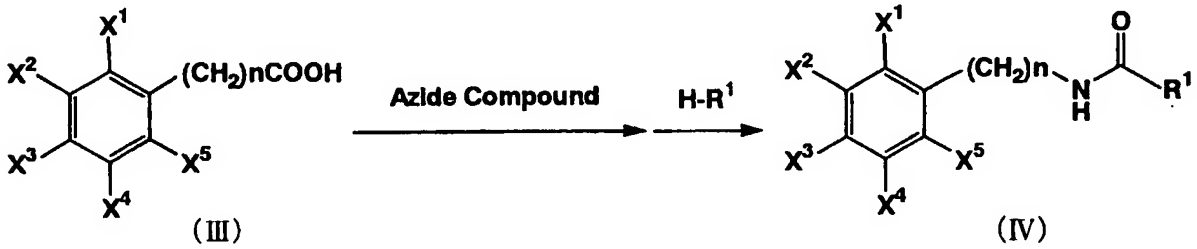
Compound Number		n	R^2	Y	R^1
731		0	H	O	
732		0	H	O	
733		0	H	O	
734		0	H	O	
735		0	H	O	
736		0	H	O	
737		0	H	O	
738		0	H	O	
739		0	H	O	
740		0	H	O	

Table-1(continued)

Compound Number		n	R^2	Y	R^1
741		0	H	O	
742		0	H	O	
743		0	H	O	
744		0	H	O	
745		0	H	O	
746		0	H	O	
747		0	H	O	
748		0	H	O	
749		0	H	O	
750		0	H	O	

The preparing methods of the compound of present invention will be explained. The carboxyamido derivatives represented by the aforementioned formula (I) can be prepared, for example, according to the method explained below.

<Preparation Method 1>

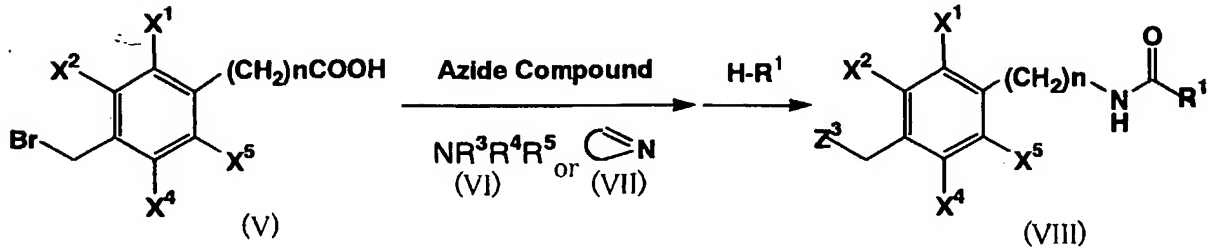


(III) (IV)

(The symbols in the scheme have the same meanings as those defined above.)

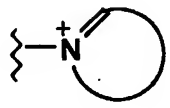
A compound represented by the formula (IV) can be obtained by reacting a carbonic acid derivative represented by the formula (III) with an azide compound such as sodium azide, trimethylsilyl azide, and diphenylphosphoryl azide at a temperature of from -50°C to 150°C for 10 minutes to 10 hours in a solvent such as tetrahydrofuran (THF), diethyl ether, or dimethylformamide (DMF) in the presence of a base such as triethylamine, pyridine, diazabicycloundecene(DBU), or potassium carbonate, and then adding 2-hydroxybenzimidazole derivatives or 2-hydroxynaphthoimidazole derivatives (H−R¹) to the mixture to allow reaction with the resulting product at a temperature of from -50°C to 150°C for 1 to 10 hours.

<Preparation Method 2>



(V) (VIII)

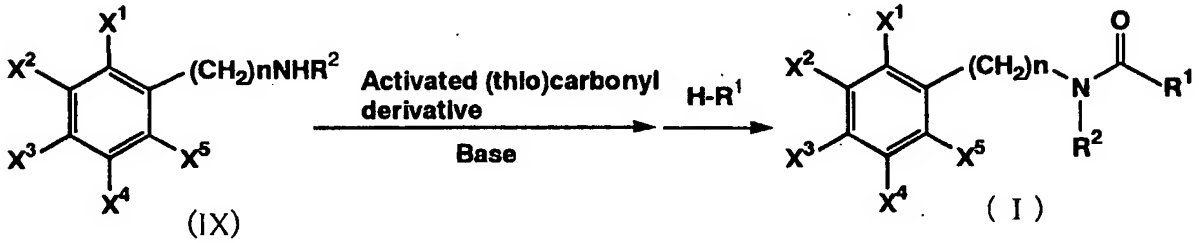
(Wherein Z^3 represents $N^+R^5R^6R^7$ or a group represented by the formula:



The other symbols in the scheme have the same meanings as those defined above.)

A compound represented by the formula (VIII) can be obtained by reacting a 4-bromomethyl derivative represented by the formula (V) with an azide compound such as sodium azide, trimethylsilyl azide, and diphenylphosphoryl azide at a temperature of from -50°C to 150°C for 10 minutes to 10 hours in a solvent such as THF, diethyl ether, or DMF in the presence of an amine compound represented by the formula (VI) or (VII), and then adding 2-hydroxybenzimidazole derivatives or 2-hydroxynaphthoimidazole derivatives ($H-R^1$) to the mixture to allow reaction with the resulting product at a temperature of from -50°C to 150°C for 1 to 10 hours.

<Preparation Method 3>



(The symbols in the scheme have the same meanings as those defined above.)

A compound represented by the formula (I) can be obtained by reacting an amine derivative represented by the formula (IX) with an activated (thio)carbonyl derivative such as triphosgene, carbonyldiimidazole, disuccimidylcarbonate and thiophosgene at a temperature of from -50°C to 50°C for 10 minutes to 24 hours in a

solvent such as THF, diethyl ether, or DMF in the presence of a base such as triethylamine, pyridine or DBU, and then adding 2-hydroxybenzimidazole derivatives or 2-hydroxynaphthoimidazole derivatives (H−R^1) to the mixture to allow reaction with the resulting product at a temperature of from -50°C to 50°C for 1 to 24 hours. In the aforementioned preparation methods, protection of a functional group and deprotection may sometimes be required. An appropriate protective groups can be chosen depending on a functional group, and reaction conditions and procedures can be chosen according to any known methods. In the aforementioned preparation methods 1 to 3, compounds of formula (III), (V), (IX) are known and commercially available, or they may be synthesized according to methods known to one of ordinary skilled in the art or can be derivatized into other compound using well known method in the art.

The medicament of the present invention have inhibitory activity against TPK1, and they inhibit TPK1 activity in Alzheimer disease and the like, thereby suppress the neurotoxicity of Aβ and the formation of PHF and inhibit the nerve cell death. Accordingly, the medicament of the present invention are useful as a medicament which radically enables preventive and/or therapeutic treatment of Alzheimer disease. In addition, the medicament of the present invention are also useful for preventive and/or therapeutic treatment of ischemic cerebrovascular accidents, Down syndrome, cerebral bleeding due to cerebral amyloid angiopathy, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration frontotemporal dementia and the like.

As the active ingredient of the medicament of the present invention, a substance may be used which is selected from the group consisting of the compound represented by the aforementioned formula (I) and a pharmacologically acceptable

salt thereof, and a solvate thereof and a hydrate thereof. The substance, per se, may be administered as the medicament of the present invention, however, it is generally desirable to administer the medicament in a form of a pharmaceutical composition which comprises the aforementioned substance as an active ingredient and one or more of pharmaceutical additives. As the active ingredient of the medicament of the present invention, two or more of the aforementioned substance may be used in combination. The above pharmaceutical composition may be supplemented with an active ingredient of other medicament for the treatment of Alzheimer disease and the like.

A type of the pharmaceutical composition is not particularly limited, and the composition may be provided as any formulation for oral or parenteral administration. For example, the pharmaceutical composition may be formulated, for example, in the form of pharmaceutical compositions for oral administration such as granules, fine granules, powders, hard capsules, soft capsules, syrups, emulsions, suspensions, solutions and the like, or in the form of pharmaceutical compositions for parenteral administrations such as injections for intravenous, intramuscular, or subcutaneous administration, drip infusions, transdermal preparations, transmucosal preparations, nasal drops, inhalants, suppositories and the like. Injections or drip infusions may be prepared as powdery preparations such as in the form of lyophilized preparations, and may be used by dissolving just before use in an appropriate aqueous medium such as physiological saline. Sustained-release preparations such as those coated with a polymer may be directly administered intracerebrally.

Types of pharmaceutical additives used for the manufacture of the pharmaceutical composition, content rations of the pharmaceutical additives relative to the active ingredient, and methods for preparing the pharmaceutical composition may be appropriately chosen by those skilled in the art. Inorganic or organic substances, or solid or liquid substances may be used as pharmaceutical additives.

Generally, the pharmaceutical additives may be incorporated in a ratio ranging from 1% by weight to 90% by weight based on the weight of an active ingredient.

Examples of excipients used for the preparation of solid pharmaceutical compositions include, for example, lactose, sucrose, starch, talc, cellulose, dextrin, kaolin, calcium carbonate and the like. For the preparation of liquid compositions for oral administration, a conventional inert diluent such as water or a vegetable oil may be used. The liquid composition may contain, in addition to the inert diluent, auxiliaries such as moistening agents, suspension aids, sweeteners, aromatics, colorants, and preservatives. The liquid composition may be filled in capsules made of an absorbable material such as gelatin. Examples of solvents or suspension mediums used for the preparation of compositions for parenteral administration, e.g. injections, suppositories, include water, propylene glycol, polyethylene glycol, benzyl alcohol, ethyl oleate, lecithin and the like. Examples of base materials used for suppositories include, for example, cacao butter, emulsified cacao butter, lauric lipid, witepsol.

Dose and frequency of administration of the medicament of the present invention are not particularly limited, and they may be appropriately chosen depending on conditions such as a purpose of preventive and/or therapeutic treatment, a type of a disease, the body weight or age of a patient, severity of a disease and the like. Generally, a daily dose for oral administration to an adult may be 0.01 to 1,000 mg (the weight of an active ingredient), and the dose may be administered once a day or several times a day as divided portions, or once in several days. When the medicament is used as an injection, administrations may preferably be performed continuously or intermittently in a daily dose of 0.001 to 100 mg (the weight of an active ingredient) to an adult.

Examples

The present invention will be explained more specifically with reference to examples. However, the scope of the present invention is not limited to the following examples. The compound number in the examples corresponds to that in the table above.

Example 1: Preparation of N-(4-aminomethylphenyl)-2-hydroxy-1H-benzimidazole-1-carboxamide hydrochloride (Compound 11)

2.60 g of N-boc-(4-aminomethyl)benzoic acid was dissolved in 50 ml of tetrahydrofuran, and the solution was added with 2.53 ml of diphenylphosphorylazide and 4.10 ml of triethylamine and the resulting mixture was heated under reflux for 1 hour. The reaction mixture was added with 1.38 g of 2-hydroxybenzimidazole and further heated under reflux for 3 hours. After the reaction was completed, the reaction mixture was cooled to room temperature, and then added with dilute hydrochloric acid and extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated and the resulting residue was added with 50 ml of ethyl acetate, and then the crystals precipitated were separated by filtration to obtain 2.40 of solid. The solid obtained was suspended in 50 ml of ethyl acetate and the suspension was added with 5 ml of a 4N hydrochloric acid/ethyl acetate solution, and then the mixture was stirred at room temperature for 5 hours. The reaction product was separated by filtration, washed with ethyl acetate, and dried to obtain 2.10 g of a pale-white solid.

Yield: 67%.

Melting point: 230-240℃ (decomposition).

NMR (DMSO-d_6, δ): 4.00 (brs, 2H), 7.12-7.20 (m, 3H), 7.47 (d, J=8.4Hz, 2H), 7.65 (d, J=8.4Hz, 2H), 8.02 (d, J=8.1Hz, 1H), 8.37 (br, 1H), 10.56 (br, 1H), 10.99 (brs, 1H).

Example 2: Preparation of N-(4-triethylaminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide bromide (Compound 679)

1.50 g of 4-bromomethylbenzoic acid was dissolved in 30 ml of tetrahydrofuran, and the solution was added with 1.80 ml of diphenylphosphorylazide and 3.88 ml of triethylamine, and the resulting mixture was heated under reflux for 1 hour. The reaction mixture was added with 1.41 g of 5,6-dichloro2-hydroxy-benzimidazole and further heated under reflux for 3 hours. After the reaction was completed, the reaction mixture was cooled to room temperature, and the deposited solid was separated by filtration and washed with 50 ml of tetrahydrofuran to obtain 2.20 g of a pale-white solid.

Yield: 61%.

Melting point: 230-233°C (decomposition).

NMR (DMSO-d_6, δ): 1.17 (t, J=7.2Hz, 9H), 3.08 (q, J=7.2Hz, 6H), 4.45 (s, 2H), 7.37 (s, 1H), 7.54 (d, J=8.4Hz, 2H), 7.73 (d, J=8.4Hz, 2H), 8.13 (s, 1H), 10.88 (brs, 1H).

Example 3: N-(4-Methylaminomethylphenyl) -2-hydroxy-1H-benzimidazole-1-carboxamide hydrochloride (Compound 43)

Melting point: 240-242°C.

NMR (DMSO-d_6, δ): 2.53 (s, 3H), 4.09 (s, 2H), 7.12-7.24 (m, 3H), 7.54 (d, J=8.7Hz, 2H), 7.67 (d, J=8.7Hz, 2H), 8.03 (d, J=8.1Hz, 1H), 9.13 (brs, 2H), 11.03 (s, 1H), 11.97 (brs, 1H).

Example 4: N-(4-Benzenesulfonylaminomethylphenyl)-2-hydroxy-1H-benzimidazole-1-carboxamide (Compound 668)

Melting point: 231-233°C.

NMR (DMSO-d_6, δ): 3.95 (d, J=6.0Hz, 2H), 7.12-7.24 (m, 5H), 7.50 (d, J=8.7Hz, 2H), 7.57-7.62 (m, 3H), 7.80 (dd, J=1.8Hz, 6.3Hz, 2H), 8.01 (d, J=6.3Hz, 1H), 8.15 (t,

J=4.2Hz, 1H), 10.91 (s, 1H), 11.87 (brs, 1H).

Example 5: N-(4-Aminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide (Compound 23)

Melting point: >300℃.

NMR (DMSO-d_6, δ): 3.99 (brs, 2H), 7.36 (s, 1H), 7.50 (d, J=8.4Hz, 2H), 7.64 (d, J=8.4Hz, 2H), 8.14 (s, 1H), 8.34 (brs, 3H), 10.76 (s, 1H), 12.97 (brs, 1H).

Example 6: N-(4-Methylaminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide hydrochloride (Compound 51)

Melting point: >300℃.

NMR (DMSO-d_6, δ): 2.52 (s, 3H), 4.08 (brs, 2H), 7.37 (s, 1H), 7.52 (d, J=8.4Hz, 2H), 7.65 (d, J=8.4Hz, 2H), 8.13 (s, 1H), 9.05 (brs, 2H), 10.79 (s, 1H), 12.29 (brs, 1H).

Example 7: N-(4-Aminomethylphenyl)-2-hydroxy-6-methyl-1H-benzimidazole-1-carboxamide hydrochloride (Compound 27)

Melting point: 238℃ (decomposition).

NMR (DMSO-d_6, δ): 2.35 (s, 3H), 4.03 (brs, 2H), 6.95-7.02 (m, 2H), 7.49 (d, J=8.4Hz, 2H), 7.65 (d, J=8.4Hz, 2H), 7.89 (s, 1H), 8.29 (br, 3H), 10.96 (s, 1H), 11.83 (brs, 1H).

Example 8: N-(4-Aminomethylphenyl)-2-hydroxy-5-methyl-1H-benzimidazole-1-carboxamide hydrochloride (Compound 31)

Melting point: 238℃ (decomposition).

NMR (DMSO-d_6, δ): 2.37 (s, 3H), 4.03 (brs, 2H), 6.95-7.02 (m, 2H), 7.49 (d, J=8.4Hz, 2H), 7.65 (d, J=8.4Hz, 2H), 7.88 (d, J=7.8Hz, 1H), 8.29 (br, 3H), 11.01 (s, 1H), 11.83 (brs, 1H).

Example 9: N-(4-Aminomethylphenyl)-6-chloro-2-hydroxy-1H-benzimidazole-1-carboxamide hydrochloride (Compound 15)

Melting point: >300°C.

NMR (DMSO-d_6, δ): 4.00 (brs, 2H), 7.13-7.27 (m, 2H), 7.51 (d, J=8.4Hz, 2H), 7.65 (d, J=8.4Hz, 2H), 7.98 (s, 1H), 8.34 (brs, 3H), 10.88 (s, 1H), 12.10 (brs, 1H).

Example 10: N-(4-Aminomethylphenyl)-5-chloro-2-hydroxy-1H-benzimidazole-1-carboxamide hydrochloride (Compound 19)

Melting point: >300°C.

NMR (DMSO-d_6, δ): 4.00 (brs, 2H), 7.13-7.28 (m, 2H), 7.51 (d, J=8.4Hz, 2H), 7.65 (d, J=8.4Hz, 2H), 8.02 (d, J=5.7Hz, 1H), 8.34 (brs, 3H), 10.86 (s, 1H), 12.13 (brs, 1H).

Example 11: N-(4-Ethylaminomethylphenyl)-2-hydroxy-1H-benzimidazole-1-carboxamide hydrochloride (Compound 101)

Melting point: 242-243°C.

NMR (DMSO-d_6, δ): 1.23 (t, J=7.0Hz, 3H), 2.94 (q, J=7.0Hz, 2H), 4.10 (brs, 2H), 7.13-7.24 (m, 3H), 7.56 (d, J=8.4Hz, 2H), 7.68 (d, J=8.4Hz, 2H), 8.05 (dd, J=1.5Hz, 7.2Hz, 1H), 9.12 (br, 2H), 11.02 (s, 1H), 11.94 (br, 1H).

Example 12: N-(4-Aminomethylphenyl)-5,6-dimethyl-2-hydroxy-1H-benzimidazole-1-carboxamide hydrochloride (Compound 35)

Melting point: >300°C.

NMR (DMSO-d_6, δ): 2.22 (s, 3H), 2.23 (s, 3H), 3.98 (brs, 2H), 6.90 (s, 1H), 7.49 (d, J=8.4Hz, 2H), 7.63 (d, J=8.4Hz, 2H), 7.81 (s, 1H), 8.41 (br, 3H), 10.98 (s, 1H), 11.78 (brs, 1H).

Example 13: N-(4-Triethylaminomethylphenyl)-2-hydroxy-1H-benzimidazole-1-carboxamide bromide (Compound 678)

Melting point: >300°C.

NMR (DMSO-d_6, δ): 1.31 (t, J=6.9Hz, 9H), 3.16 (q, J=6.9Hz, 6H), 4.46 (brs, 2H), 7.13-7.23 (m, 3H), 7.53 (d, J=8.7Hz, 2H), 7.76 (d, J=8.7Hz, 2H), 8.03 (d, J=8.1Hz, 1H), 11.12 (s, 1H).

Example 14: N-(4-(N-tert-Butoxycarbonyl-N-methyl)aminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide (Compound 655)

Melting point: 226-227°C.

NMR (DMSO-d_6, δ): 1.42 (brs, 9H), 2.76 (s, 3H), 4.35 (s, 2H), 7.24 (d, J=8.4Hz, 2H), 7.35 (s, 1H), 7.57 (d, J=8.4Hz, 2H), 8.15 (s, 1H), 10.70 (s, 1H).

Example 15: N-(4-Decanoylaminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide (Compound 644)

Melting point: 204-206°C (decomposition).

NMR (DMSO-d_6, δ): 0.85 (t, J=6.3Hz, 3H), 1.24 (brs, 12H), 1.53 (m, 2H), 2.12 (t, J=7.2Hz, 2H), 4.23 (d, J=5.7Hz, 2H), 7.26 (d, J=8.4Hz, 2H), 7.35 (s, 1H), 7.53 (d, J=8.4Hz, 2H), 8.15 (s, 1H), 10.69 (brs, 1H).

Example 16: N-(4-(N-Benzyloxycarbonyl-N-methyl)aminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide (Compound 657)

Melting point: 227-229°C (decomposition).

NMR (DMSO-d_6, δ): 2.81 (s, 3H), 4.44 (brs, 2H), 5.12 (s, 2H), 7.25-7.37 (m, 8H), 7.56 (m, 2H), 8.15 (s, 1H), 10.72 (brs, 1H), 12.19 (br, 1H).

Example 17: N-(4-(N-Benzenesulfonyl-N-methyl)aminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide (Compound 671)

Melting point: 203-208℃.

NMR (DMSO-d_6, δ): 2.56 (s, 3H), 4.12 (s, 2H), 7.35 (s, 1H), 7.59 (d, J=8.7Hz, 2H), 7.66-7.79 (m, 3H), 7.86 (dd, J=1.5Hz, 8.4Hz, 2H), 8.15 (s, 1H), 10.74 (brs, 1H).

Example 18: N-(4-(N-Butyryl-N-methyl)aminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide (Compound 633)

Melting point: 221-224℃ (decomposition).

NMR (DMSO-d_6, δ): 0.87 (m, 3H), 1.55 (m, 2H), 2.34 (m, 2H), 2.81 (s, 1H), 2.91 (s, 2H), 4.48 (s, 1.4H), 4.55 (s, 0.6H), 7.23 (m, 2H), 7.35 (s, 1H), 7.57 (m, 2H), 8.14 (s, 1H), 10.70 (brs, 1H).

Example 19: N-(4-Tripropylaminomethylphenyl)-2-hydroxy-1H-benzimidazole-1-carboxamide bromide (Compound 680)

Melting point: 215-216℃.

NMR (DMSO-d_6, δ): 0.92 (t, J=7.2Hz, 9H), 1.76 (m, 6H), 3.05 (m, 6H), 4.51 (s, 2H), 7.13-7.26 (m, 3H), 7.50 (d, J=8.4Hz, 2H), 7.78 (d, J=8.4Hz, 2H), 8.03 (d, J=7.2Hz, 1H), 11.12 (s, 1H), 11.92 (brs, 1H).

Example 20: N-(4-Tributylaminomethylphenyl)-2-hydroxy-1H-benzimidazole-1-carboxamide bromide (Compound 682)

Melting point: 200-201℃.

NMR (DMSO-d_6, δ): 0.96 (t, J=1.8Hz, 9H), 1.33 (m, 6H), 3.09 (m, 6H), 3.29 (m, 6H), 4.51 (s, 2H), 7.13-7.23 (m, 3H), 7.51 (d, J=8.4Hz, 2H), 7.77 (d, J=8.4Hz, 2H), 8.03 (d, J=6.9Hz, 1H), 11.10 (s, 1H), 11.89 (brs, 1H).

Example 21: N-(4-(Cyclohexyldimethyl)aminomethylphenyl)-2-hydroxy-1H-benzimidazole-1-carboxamide bromide (Compound 684)

Melting point: 231-233°C.

NMR (DMSO-d_6, δ): 1.10-1.40 (m, 3H), 1.45-1.68 (m, 3H), 1.89-1.94 (m, 2H), 2.26-2.31 (m, 2H), 2.88 (s, 7H), 4.49 (s, 2H), 7.13-7.26 (m, 3H), 7.58 (d, J=8.4Hz, 2H), 7.76 (d, J=8.4Hz, 2H), 8.03 (d, J=7.8Hz, 1H), 11.10 (s, 1H), 11.93 (brs, 1H).

Example 22: N-(4-(Benzyldimethyl)aminomethylphenyl)-2-hydroxy-1H-benzimidazole-1-carboxamide bromide (Compound 688)

Melting point: 221-222°C.

NMR (DMSO-d_6, δ): 2.87 (s, 6H), 4.58 (s, 4H), 7.13-7.24 (m, 3H), 7.52-7.63 (m, 7H), 7.78 (d, J=8.7Hz, 2H), 8.03 (d, J=7.5Hz, 1H), 11.11 (s, 1H), 11.92 (brs, 1H).

Example 23: N-(4-(4-Methyl-4-morpholinyl)methylphenyl)-2-hydroxy-1H-benzimidazole-1-carboxamide bromide (Compound 704)

Melting point: 207-208°C.

NMR (DMSO-d_6, δ): 3.06 (s, 3H), 3.49-3.60 (m, 4H), 3.90-3.99 (m, 4H), 4.66 (s, 2H), 7.13-7.26 (m, 3H), 7.59 (d, J=8.4Hz, 2H), 7.77 (d, J=8.4Hz, 2H), 8.03 (d, J=8.1Hz, 1H), 11.12 (s, 1H), 11.94 (br, 1H).

Example 24: N-(4-(4-Butyl-4-morpholinyl)methylphenyl)-2-hydroxy-1H-benzimidazole-1-carboxamide bromide (Compound 710)

Melting point: 208-209°C.

NMR (DMSO-d_6, δ): 0.95 (t, J=7.2Hz, 3H), 1.33 (m, 2H), 1.77 (m, 2H), 3.33-3.46 (m, 6H), 3.98 (brs, 4H), 4.67 (s, 2H), 7.10-7.26 (m, 3H), 7.54 (d, J=8.4Hz, 2H), 7.77 (d, J=8.4Hz, 2H), 8.03 (d, J=6.9Hz, 1H), 11.11 (s, 1H), 11.92 (s, 1H).

Example 25: N-(4-(4-Octyl-4-morpholinyl)methylphenyl)-2-hydroxy-1H-benzimidazole-1-carboxamide bromide (Compound 714)

Melting point: 182-184℃.

NMR (DMSO-d_6, δ): 0.88 (m, 3H), 1.28-1.35 (m, 12H), 3.38-3.42 (m, 6H), 3.98 (brs, 4H), 4.68 (s, 2H), 7.13-7.23 (m, 3H), 7.53 (d, J=8.4Hz, 2H), 7.78 (d, J=8.4Hz, 2H), 8.03 (d, J=6.9Hz, 1H), 11.12 (s, 1H), 11.93 (s, 1H).

Example 26: N-(4-(4-dimethylamino-1-pyridyl)methylphenyl)-2-hydroxy-1H-benzimidazole-1-carboxamide bromide (Compound 719)

Melting point: 230-231℃.

NMR (DMSO-d_6, δ): 3.18 (s, 6H), 5.37 (s, 2H), 6.93 (t, J=6.9Hz, 2H), 7.04-7.23 (m, 7H), 7.45 (d, J=8.4Hz, 2H), 7.66 (d, J=8.4Hz, 2H), 8.40 (d, J=7.5Hz, 1H), 10.99 (s, 1H), 11.93 (br, 1H).

Example 27: N-(3-Aminomphenyl)-2-hydroxy-1H-benzimidazole-1-carboxamide (Compound 2)

Melting point: >300℃.

NMR (DMSO-d_6, δ): 7.03-7.23 (m, 5H), 7.35-7.42 (m, 3H), 7.71 (brs, 1H), 8.01 (d, J=7.8Hz, 1H), 11.04 (s,1H), 11.95 (s, 1H).

Example 28: N-(4-(Benzyldimethylamino)methylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide bromide (Compound 689)

Melting point: 233-236℃.

NMR (DMSO-d_6, δ): 2.87 (s, 6H), 4.60 (s, 4H), 7.39 (s, 1H), 7.51-7.64 (m, 7H), 7.76 (d, J=8.4Hz, 2H), 8.15 (s, 1H), 10.91 (s, 1H), 12.20 (s, 1H).

Example 29: N-(4-(Cyclohexyldimethylamino)methylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide bromide (Compound 685)

Melting point: 230-234℃.

NMR (DMSO-d_6, δ): 1.00-1.30 (m, 3H), 1.40-1.62 (m, 3H), 1.80-1.90 (m, 2H), 2.10-2.30 (m, 2H), 2.83 (s, 6H), 4.42 (s, 2H), 6.95 (s, 1H), 7, 48 (d, J=8.7Hz, 2H), 7.66 (d, J=8.7Hz, 2H), 7.80 (s, 1H), 12.74 (s, 1H).

Example 30: N-(4-(4-Dimethylamino-1-pyridyl)methylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide diphenylphosphonate (Compound 720)

Melting point: 235-239℃.

NMR (DMSO-d_6, δ): 3.14 (s, 6H), 5.33 (s, 2H), 6.86-7.19 (m, 12H), 7.32 (s, 1H), 7.41 (d, J=8.7Hz, 2H), 7.61 (d, J=8.7Hz, 2H), 8.08 (s, 1H), 8.36 (d, J=7.5Hz, 2H), 10.80 (s, 1H).

Example 31: N-(4-Tributylaminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide bromide (Compound 683)

Melting point: 239-241℃.

NMR (DMSO-d_6, δ): 0.96 (t, 9H, J=7.2Hz), 1. 33 (m, 6H), 1.73 (m, 6H), 3.08 (m, 6H), 4.48 (s, 2H), 6.99 (s, 1H), 7.46 (d, J=8.4Hz, 2H), 7.72 (d, J=8.4Hz, 2H), 7.83 (s, 1H), 12.80 (s, 1H).

Example 32: N-(4-Tripropylaminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide bromide (Compound 681)

Melting point: 225-227℃.

NMR (DMSO-d_6, δ): 0.92 (t, J=7.2Hz, 9H), 1. 77 (m, 6H), 3.06 (m, 6H), 4.51 (s, 2H), 7.38 (s, 1H), 7.51 (s, 1H), 7.77 (d, J=8.7Hz2H), 8.14 (d, J=8.7Hz, 2H), 8.14 (s, 1H), 10.95 (s, 1H).

Example 33: N-(4-(4-Methyl-4-morpholinyl)methylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide chloride (Compound 705)

Melting point: 220-221℃.

NMR (DMSO-d_6, δ): 3.06 (s, 3H), 3.52 (m, 4H), 3.98 (m, 4H), 4.67 (s, 2H), 7.37 (s, 1H), 7. 59 (d, J=8.4Hz, 2H), 7.76 (d, J=8.4Hz, 2H), 8.13 (s, 1H), 11.00 (s, 1H).

Example 34: N-(4-Methylaminomethylphenyl)-2-hydroxy-1H-naphthoimidazole-1-carboxamide (Compound 61)

Melting point: 242-245℃ (decomposition).

NMR (DMSO-d_6, δ): 2.56 (s, 3H), 4.11 (s, 2H), 7.39-7.48 (m, 2H), 7.52–7.55 (m, 3H), 7.73 (d, J=8.4Hz, 2H), 7.92-7.99 (m, 2H), 8.50 (s, 1H), 8.91 (br, 2H), 10.93 (s, 1H), 12.09 (brs, 1H).

Example 35: N-(4-Morpholinylmethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide (Compound 534)

Melting point: 231-234℃ (decomposition).

NMR (DMSO-d_6, δ): 2.36 (brs, 4H), 3.45 (s, 2H), 3.56-3.59 (m, 4H), 7.32 (d, J=8.1Hz, 2H), 7.35 (s, 1H), 7.54 (d, J=8.1Hz, 2H), 8.14 (s, 1H), 10.70 (s, 1H).

Example 36: N-(4-Butylaminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide hydrochloride (Compound 119)

Melting point: 242℃ (decomposition).

NMR (DMSO-d_6, δ): 0.89 (t, J=7.5Hz, 3H), 1. 33 (m, 2H), 1.62 (m, 2H), 2.89 (t, J=7.8Hz, 2H), 4.12 (s, 2H), 7.38 (s, 1H), 7.55 (d, J=8. 7Hz, 2H), 7.67 (d, J=8.7Hz, 2H), 8.15 (s, 1H), 8.90 (br, 2H), 10.80 (s, 1H), 11.96 (br, 1H).

Example 37: N-(4-Dimethylaminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide hydrochloride (Compound 133)

Melting point: >300℃.

NMR (DMSO-d_6, δ): 2.69 (s, 6H), 4.25 (s, 2H), 7.38 (s, 1H), 7.57 (d, J=8.4Hz, 2H), 7.69 (d, J=8.4Hz, 2H), 8.14 (s, 1H), 9.06 (br, 1H), 10.83 (s, 1H).

Example 38: N-(4-(1-Piperidyl)methylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide hydrochloride (Compound 470)

Melting point: 273-275℃.

NMR (DMSO-d_6, δ): 2.27-3.41 (m, 10H), 4.23 (s, 2H), 7.39 (s, 1H), 7.56 (d, J=8.4Hz, 2H), 7.70 (d, J=8.4Hz, 2H), 8.15 (s, 1H), 10.83 (s, 1H).

Example 39: N-(4-(4-Methyl-1-piperadyl)methylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide hydrochloride (Compound 537)

Melting point: 242-244℃ (decomposition).

NMR (DMSO-d_6, δ): 2.81 (s, 3H), 3.38-3.58 (m, 8H), 4.23 (br, 2H), 7.38 (s, 1H), 7.59 (br, 2H), 7.68 (d, J=8.7Hz, 2H), 8.15 (s, 1H), 10.81 (s, 1H), 12.28 (s, 1H).

Example 40: N-(4-(2-Dimethylaminoethyl)aminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide 2hydrochloride (Compound 175)

Melting point: 220-221℃ (decomposition).

NMR (DMSO-d_6, δ): 2.83 (s, 6H), 3.41-3.46 (m, 4H), 4.18 (s, 2H), 7.36 (s, 1H), 7.59 (d, J=8.7Hz, 2H), 7.66 (d, J=8.7Hz, 2H), 8.12 (s, 1H), 9.65 (br, 2H), 10.78 (s, 1H), 12.28 (br, 1H).

Example 41: N-(4-Cyclohexylmethylaminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide hydrochloride (Compound 217)

Melting point: 242℃ (decomposition).

NMR (DMSO-d_6, δ): 0.91-0.99 (m, 2H), 1.16-1.23 (m, 3H), 1.63-1.77 (m, 6H), 2.75 (d, J=6.6Hz, 2H), 4.12 (s, 2H), 7.38 (s, 1H), 7.55 (d, J=8.7Hz, 2H), 7.68 (d, J=8.7Hz, 2H), 8. 15 (s, 1H), 8.80 (br, 1H), 10.80 (s, 1H), 11. 98 (br, 1H).

Example 42: N-(4-Benzylaminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide hydrochloride (Compound 221)

Melting point: 227℃. (decomposition).

NMR (DMSO-d_6, δ): 4.17 (brs, 4H), 7.38 (s, 1H), 7.39-7.56 (m, 7H), 7.68 (d, J=8.4Hz, 2H), 8.15 (s, 1H), 9.35 (br, 1H), 10.80 (s, 1H), 11.96 (br, 1H).

Example 43: N-(4-Heptylaminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide hydrochloride (Compound 128)

Melting point: 231℃ (decomposition).

NMR (DMSO-d_6, δ): 0.83 (m, 3H), 1.22 (m, 8H), 1.58 (m, 2H), 2.83 (t, J=7.8Hz, 2H), 4.07 (s, 2H), 7.34 (s, 1H), 7.50 (d, J=8.4Hz, 2H), 7.63 (d, J=8.4Hz, 2H), 8.11 (s, 1H), 8.90 (br, 2H), 10.76 (s, 1H), 12.21 (br, 1H).

Example 44: N-(4-(3-Pyridylmethyl)aminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide 2hydrochloride (Compound 232)

Melting point: 212℃ (decomposition).

NMR (DMSO-d_6, δ): 4.20 (brs, 2H), 4.31 (brs, 2H), 7.39 (s, 1H), 7.58 (d, J=8.4Hz, 2H), 7.66-7.80 (m, 3H), 8.15 (s, 1H), 8.26 (d, J=8.1Hz, 2H), 8.73 (dd, J=1.2Hz, 5.1Hz, 1H), 8.85 (s, 1H), 9.69 (br, 2H), 10.81 (s, 1H), 11.17 (s, 1H).

Example 45: N-(4-(2-Pyridylethyl)aminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide 2hydrochloride (Compound 237)

Melting point: 225℃ (decomposition).

NMR (DMSO-d_6, δ): 3.37 (m, 4H), 4.20 (brs, 2H), 7.39 (s, 1H), 7, 58-7.70 (m, 6H), 8.12-8.18 (m, 2H), 8.68 (d, J=5.1Hz, 2H), 9.46 (br, 2H), 10.80 (s, 1H), 12.30 (s, 1H).

Example 46: N-(4-Dimethylaminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide (Compound 143)

Melting point: 205℃ (decomposition).

NMR (DMSO-d_6, δ): 1.01 (t, J=7.2Hz, 6H), 2. 53 (q, J=7.2Hz, 4H), 3.60 (s, 2H), 7.30-7.36 (m, 3H), 7.55 (d, J=8.1Hz, 2H), 8.12 (s, 1H), 10.87 (s, 1H).

Example 47: N-(4-(3-Hydroxypropyl)aminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide hydrochloride (Compound 155)

Melting point: 225℃ (decomposition).

NMR (DMSO-d_6, δ): 1.92-2.02 (m, 2H), 2.99 (m, 2H), 4.08 (t, J=6.3Hz, 2H), 4.14 (brs, 2H), 7.38 (s, 1H), 7.54 (d, J=8.7Hz, 2H), 7.68 (d, J=8.7Hz, 2H), 8.15 (s, 1H), 8.94 (br, 2H), 10.81 (s, 1H), 12.25 (s, 1H).

Example 48: N-(4-bis(2-Hydroxyethyl)aminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide hydrochloride (Compound 161)

Melting point: 217℃ (decomposition).

NMR (DMSO-d_6, δ): 3.05 (m, 4H), 3.58 (m, 4H), 4.12 (brs, 2H), 5.33 (br, 2H), 7.39 (s, 1H), 7.61 (d, J=8.4Hz, 2H), 7.70 (d, J=8.4Hz, 2H), 8.15 (s, 1H), 9.55 (br, 1H), 10.83 (s, 1H), 12.26 (s, 1H).

Example 49: N-(4-(2-Pyridylmethyl)aminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide 2hydrochloride (Compound 231)

Melting point: 218℃ (decomposition).

NMR (DMSO-d_6, δ): 4.23 (s, 2H), 4.30 (s, 2H), 7.39 (s, 1H), 7.46 (m, 1H), 7.54 (m, 3H), 7. 68 (d, J=8.7Hz, 2H), 7.91 (m, 1H), 8.15 (s, 1H), 8.66 (d, J=5.1Hz, 1H), 9.64 (br, 2H), 10.81 (s, 1H), 12.30 (s, 1H).

Example 50: N-(4-(2-Dimethylaminoethyl)aminomethylphenyl)-2-hydroxy-1H-benzimidazole-1-carboxamide 2hydrochloride (Compound 173)

Melting point: 228℃ (decomposition).

NMR (DMSO-d_6, δ): 2.84 (s, 6H), 3.20-3.50 (m, 4H), 4.19 (s, 2H), 7.10-7.25 (m, 3H), 7.58 (d, J=8.7Hz, 2H), 7.66 (d, J=8.7Hz, 2H), 8.03 (d, J=8.4Hz, 2H), 9.46 (br, 2H), 10.60 (br, 1H), 11.03 (s, 1H), 11.91 (s, 1H).

Example 51: N-(4-Dipropylaminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide (Compound 147)

Melting point: 197℃ (decomposition).

NMR (DMSO-d_6, δ): 0.82 (t, J=7.5Hz, 6H), 1. 43 (m, 4H), 2:34 (t, J=7.5Hz, 6H), 3.53 (s, 2H), 7.32 (d, J=8.1Hz, 2H), 7.33 (s, 1H), 7.52 (d, J=8.1Hz, 2H), 8.13 (s, 1H), 10.78 (s, 1H).

Example 52: N-Methyl-N-(4-methylaminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide methanesulfonate (Compound 57)

Melting point: 146-148℃ (decomposition).

NMR (DMSO-d_6, δ): 2.88 (s, 3H), 3, 45 (s, 3H), 3.39 (br, 3H), 4.06 (br, 2H), 7.18 (s, 1H), 7.37-7.45 (m, 4H), 7.59 (s, 1H), 8.66 (br, 2H), 11.27 (s, 1H).

Example 53: N-(4-(N-Benzyl-N-methyl)aminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide (Compound 223)

Melting point: 207-208℃.

NMR (DMSO-d_6, δ): 4.02 (s, 2H), 4.24 (s, 2H), 7.20–7.40 (m, 8H), 7.57 (d, J=8.1Hz, 2H), 8.15 (s, 1H), 10.74 (brs, 1H).

Example 54: N-(4-(2-(4-Morpholinyl)ethyl)aminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide 2hydrochloride (Compound 404)

Melting point: 218℃ (decomposition).

NMR (DMSO-d_6, δ): 3.00-4.00 (m, 12H), 4.19 (brs, 2H), 7.39 (s, 1H), 7.59 (d, J=8.4Hz, 2H), 7.69 (d, J=8.4Hz, 2H), 8.15 (s, 1H), 9.45 (br, 2H), 10.81 (s, 1H), 11.05 (br, 1H), 12.28 (brs, 1H).

Example 55: N-(4-(N-Methyl-N-(2-methylaminoethyl))aminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide 2hydrochloride (Compound 195)

Melting point: 233℃ (decomposition).

NMR (DMSO-d_6, δ): 2.60 (brs, 3H), 2.72 (br, 3H), 3.40 (br, 4H), 3.46 (br, 1H), 4.34 (br, 1H), 7.39 (s, 1H), 7.55-7.75 (m, 4H), 8.15 (s, 1H), 9.07 (br, 1H), 10.53 (brs, 1H), 10.95 (br, 1H), 12.28 (s, 1H).

Example 56: N-(4-(2-Methylaminoethyl)aminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide 2hydrochloride (Compound 169)

Melting point: 225℃ (decomposition).

NMR (DMSO-d_6, δ): 2.63 (s, 3H), 3.30 (brs, 4H), 4.19 (brs, 2H), 7.38 (s, 1H), 7.60 (d, J=8.7Hz, 2H), 7.68 (d, J=8.7Hz, 2H), 8.15 (s, 1H), 9.23 (br, 2H), 9.62 (br, 2H), 10.82 (s, 1H), 12.27 (s, 1H).

Example 57: N-(4-(2-(1-Piperidyl)ethyl)aminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide 2hydrochloride (Compound 360)

Melting point: 233℃ (decomposition).

NMR (DMSO-d_6, δ): 1.40 (m, 1H), 1.60-1.95 (m, 5H), 2.93 (m, 2H), 3.40-3.70 (m, 6H), 4.19 (s, 2H), 7.39 (s, 1H), 7.60 (d, J=8.4Hz, 2H), 7.69 (d, J=8.4Hz, 2H), 8.16 (s, 1H), 9.55 (br, 1H), 10.47 (br, 1H), 10.81 (s, 1H), 12. 29 (br, 1H).

Example 58: N-(4-(4-Piperidyl)methylaminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide 2hydrochloride (Compound 300)

Melting point: 222℃ (decomposition).

NMR (DMSO-d_6, δ): 1.40 (m, 2H), 1.94 (m, 2H), 2.05 (m, 1H), 2.83 (m, 4H), 3.26 (m, 2H)4.12 (s, 2H), 7.39 (s, 1H), 7.61 (d, J=8.7Hz, 2H), 7.67 (d, J=8.7Hz, 2H), 8.15 (br, 1H), 8.72 (br, 1H), 8.93 (br, 1H), 9.32 (br, 1H), 10. 86 (s, 1H), 12.32 (s, 1H).

Example 59: N-(4-Methylaminomethylbenzyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide (Compound 53)

Melting point: 278-280℃ (decomposition).

NMR (DMSO-d_6, δ): 2.49 (s, 3H), 4.06 (s, 2H), 4.52 (d, J=5.7Hz, 2H), 7.30 (s, 1H), 7.40 (d, J=8.1Hz, 2H), 7.46 (d, J=8.1Hz, 2H), 8.06 (s, 1H), 9.00–9.10 (m, 3H), 12.05 (brs, 1H).

Example 60: N-(4-Methylaminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-thiocarboxamide hydrochloride (Compound 52)

Melting point: >300℃.

NMR (DMSO-d_6, δ): 2.58 (s, 3H), 4.15 (s, 2H), 7.36 (s, 1H), 7.58 (d, J=8.1Hz, 2H), 7.82 (d, J=8.1Hz, 2H), 8.32 (s, 1H), 8.91 (br, 2H), 12.08 (brs, 1H), 12.31 (brs, 1H).

Example 61: N-(2-Bromo-4-methylaminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-thiocarboxamide hydrochloride (Compound 70)

Melting point: 245-250℃ (decomposition).

NMR (DMSO-d_6, δ): 2.55 (s, 3H), 4.17 (s, 2H), 7.30-7.37 (m, 2H), 7.59-7.62 (m, 2H), 8.83 (s, 1H), 8.12.30 (br, 2H).

Example 62: N-(4-(1-Piperidyl)methylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-thiocarboxamide hydrochloride (Compound 532)

Melting point: 173-178℃ (decomposition).

NMR (DMSO-d_6, δ): 1.64-1.90 (m, 6H), 2.87 (m, 2H), 3.28 (m, 2H), 4.28 (s, 2H), 7.57-7.71 (m, 3H), 7.89 (d, J=8.1Hz, 2H), 8.29 (s, 1H), 10.25 (br, 1H), 12.10 (brs, 1H), 12.36 (brs, 1H).

Example 63: N-(4-(2-Methylaminoethyl)phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide hydrochloride (Compound 547)

Melting point: 232-234℃.

NMR (DMSO-d_6, δ): 2.55 (s, 3H), 2.92 (m, 2H), 3.10 (m, 2H), 7.27 (d, J=5.1Hz, 2H), 7.34 (s, 1H), 7.54 (d, J=5.1Hz, 2H), 8.11 (s, 1H), 8.96 (s, 1H), 10.68 (s, 1H).

Example 64: N-(2-Methylaminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide hydrochloride (Compound 97)

Melting point: 236-238℃.

NMR (DMSO-d_6, δ): 2.58 (s, 3H), 4.16 (m, 2H), 7.33 (dd, J=7.5, 7.5Hz, 1H), 7.36 (s, 1H), 7.49 (dd, J=7.5, 7.5Hz, 1H), 7.62 (d, J=7.5Hz, 1H), 7.76 (d, J=7.5Hz, 1H), 8.12 (s, 1H), 9.11 (s, 1H), 10.54 (s, 1H).

Example 65: N-(3-Methylaminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide hydrochloride (Compound 83)

Melting point: 186-188℃.

NMR (DMSO-d_6, δ): 2.53 (s, 3H), 4.12 (m, 2H), 7.32 (d, J=7.5Hz, 1H), 7.36 (s, 1H),

7.49 (dd, J=7.5, 7.5Hz, 1H), 7.69 (m, 2H), 8.12 (s, 1H), 9.23 (s, 1H), 10.80 (s, 1H).

Example 66: N-(3-Methylaminomethylphenyl)-2-hydroxy-1H-naphth[2,3-d]imidazole-1-carboxamide hydrochloride (Compound 85)

Melting point: 252-254℃.

NMR (DMSO-d_6, δ): 2.57 (s, 3H), 4.15 (m, 2H), 7.29 (d, J=7.8Hz, 1H), 7.39-7.51 (m, 5H), 7.55 (s, 1H), 7.75 (d, J=8.7Hz, 1H), 7.94 (m, 2H), 8.50 (s, 1H), 8.98 (s, 1H), 10.94 (s, 1H), 12.13 (s, 1H).

Example 67: N-(2-Methylaminomethylphenyl)-2-hydroxy-1H-naphth[2,3-d]imidazole-1-carboxamide hydrochloride (Compound 99)

Melting point: 241-243℃.

NMR (DMSO-d_6, δ): 2.63 (s, 3H), 4.22 (m, 2H), 7.36-7.60 (m, 6H), 7.90 (d, J=8.4Hz, 1H), 7.96 (m, 2H), 8.48 (s, 1H), 8.83 (s, 1H), 10. 69 (s, 1H), 12.11 (s, 1H).

Example 68: N-(3-Methyl-4-methylaminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide (Compound 75)

Melting point: 234-236℃.

NMR (DMSO-d_6, δ): 2.39 (s, 3H), 2.61 (s, 3H), 4.10 (m, 2H), 7.37 (s, 1H), 7.43-7.55 (m, 3H), 8.15 (s, 1H), 8.79 (s, 1H), 10.74 (s, 1H)

Example 69: N-(2-Methyl-5-isoindolinyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide (Compound 605)

Melting point: 245-247℃.

NMR (DMSO-d_6, δ): 2.99 (s, 3H), 4.58 (d, J=12.9Hz, 4H), 7.37 (s, 1H), 7.41 (d, J=8.4Hz, 1H), 7.52 (d, J=8.4Hz, 1H), 7.72 (s, 1H), 8. 12 (s, 1H), 10.79 (s, 1H).

Example 70: N-(4-(3-Methylaminopropoxy)phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide (Compound 580)

Melting point: 209-211℃.

NMR (DMSO-d_6, δ): 2.06 (m, 2H), 2.56 (s, 3H), 3.04 (t, J=7.5Hz, 2H), 4.05 (t, J=7.5Hz, 2H), 6.97 (d, J=7.2Hz, 2H), 7.35 (s, 1H), 7.49 (d, J=7.2Hz, 2H), 8.12 (s, 1H), 8.79 (s, 1H), 10.53 (s, 1H).

Example 71: N-(3,4-Bis(2-methylaminoethoxy)phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide 2hydrochloride (Compound 577)

Melting point: 233-234℃.

NMR (DMSO-d_6, δ): 2.64 (s, 6H), 4.25 (m, 8H), 7.11 (d, J=9.0Hz, 1H), 7.18 (d, J=9.0Hz, 1H), 7.37 (s, 1H), 7.39 (s, 1H), 8.13 (s, 1H), 10.62 (s, 1H).

Example 72: N-(4-(3-dimethylaminopropylamino)methylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide 2hydrochloride (Compound 183)

Melting point: 170℃ (decomposition).

NMR (DMSO-d_6, δ): 2.10 (m, 2H), 2.74 (d, J=4.8Hz, 6H), 2.99 (m, 2H), 3.15 (m, 2H), 4.13 (br, 2H), 7.39 (s, 1H), 7.59 (d, J=8.4Hz, 2H), 7.67 (d, J=8.4Hz, 2H), 8.15 (s, 1H), 9.34 (br, 2H), 10.44 (br, 1H), 10.80 (s, 1H), 12.23 (s, 1H).

Example 73: N-(4-(4-aminomethyl-1-pyperidinylmethyl)phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide 2hydrochloride (Compound 486)

Melting point: 242℃ (decomposition).

NMR (DMSO-d_6, δ): 1.40-1.60 (m, 2H), 1.70-2.00 (m, 3H), 2.72 (m, 2H), 2.90 (m, 2H), 3.33 (m, 2H), 4.24 (br, 2H), 7.39 (s, 1H), 7.61 (d, J=8.1Hz, 2H), 7.70 (d, J=8.1Hz, 2H), 8.02 (br, 3H), 8.15 (s, 1H), 10.46 (br, 1H), 10.83 (s, 1H), 12.30 (br, 1H).

Example 74: N-(4-(2-diisopropylaminoethylamino)methylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide 2hydrochloride (Compound 189)

Melting point: 199-200℃.

NMR (DMSO-d_6, δ): 1.32 (d, J=6.3Hz, 6H), 1.36 (d, J=6.3Hz, 6H), 3.44 (m, 2H), 3.72 (m, 2H), 4.23 (d, J=4.5Hz, 2H), 7.39 (s, 1H), 7.61 (d, J=8.7Hz, 2H), 7.69 (d, J=8.7Hz, 2H), 8.15 (s, 1H), 9.79 (br, 1H), 9.87 (br, 1H), 10.24 (br, 1H), 10.81 (s, 1H), 12.29 (s, 1H).

Example 75: N-(4-(2-(1-pyperadinyl)ethylamino)methylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide 3hydrochloride (Compound 388)

Melting point: 218℃ (decomposition).

NMR (DMSO-d_6, δ): 3.00-3.60 (m, 12H), 4.18 (dulls, 2H), 7.38 (s, 1H), 7.61 (d, J=8.7Hz, 2H), 7.68 (d, J=8.7Hz, 2H), 8.15 (s, 1H), 9.51 (br, 3H), 10.80 (s, 1H), 12.35 (s, 1H).

Example 76: N-(4-(4-(2-aminoethyl)-1-pyperadinylmethyl)phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide 3hydrochloride (Compound 538)

Melting point: 212-214℃.

NMR (DMSO-d_6, δ): 2.60-3.80 (m, 12H), 4.33 (br, 2H), 7.38 (s, 1H), 7.60-7.75 (m, 4H), 7.95 (br, 2H), 8.15 (s, 1H), 10.80 (s, 1H), 12.30 (s, 1H).

Example 77: N-(4-(3-dimethylaminomethyl-1-pyperidinylmethyl)phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide (Compound 485)

Melting point: 112-113℃.

NMR (DMSO-d_6, δ): 0.89 (br, 1H), 1.40-1.83 (m, 5H), 1.96 (m, 1H), 2.00-2.20 (m, 8H), 2.70 (m, 1H), 2.81 (m, 1H), 3.53 (s, 2H), 7.28-7.32 (m, 3H), 7.53 (d, J=8.4Hz, 2H), 8.10 (s, 1H), 11.00 (s, 1H).

Example 78: N-(4-(4-dimethylamino-1-pyperidinylmethyl)phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide (Compound 479)

Melting point: 208-210℃.

NMR (DMSO-d_6, δ): 1.30-1.55 (m, 2H), 1.60-1.80 (m, 2H), 1.80-2.00 (m, 2H), 2.30 (m, 7H), 2.85 (m, 2H), 4.04 (s, 2H), 7.25 (s, 1H), 7.24 (d, J=8.4Hz, 2H), 7.53 (d, J=8.4Hz, 2H), 8.07 (s, 1H), 11.22 (s, 1H).

Example 79: N-(4-(((3-pyperidinylmethyl)amino)methyl)phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide 2hydrochloride (Compound 296)

Melting point: 213℃ (decomposition).

NMR (DMSO-d_6, δ): 1.20 (m, 1H), 1.63 (m, 1H), 1.70-1.95 (m, 2H), 2.13 (m, 1H), 2.60-3.05 (m, 5H), 3.18 (m, 1H), 2.13 (dulls, 2H), 7.39 (s, 1H), 7.59 (d, J=8.4Hz, 2H), 7.68 (d, J=8.4Hz, 2H), 8.16 (s, 1H), 9.00 (br, 2H), 9.28 (br, 2H), 10.82 (dulls, 1H), 12.29 (s, 1H).

Example 80: N-(4-(4-dimethylaminomethyl-1-pyperidinylmethyl)phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide 2hydrochloride (Compound 488)

Melting point: 227-229℃.

NMR (DMSO-d_6, δ): 1.09 (m, 2H), 1.45 (br, 1H), 1.64 (m, 2H), 1.94 (m, 2H), 2.13 (m, 2H), 2.17 (s, 6H), 2.80 (m, 2H), 3.45 (s, 2H), 7.20-7.31 (m, 3H), 7.53 (d, J=8.4Hz, 2H), 8.09 (s, 1H), 11.10 (dulls, 1H).

Example 81: N-(4-(4-(2-dimethylaminoethyl)-1-pyperidinylmethyl)phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide 2hydrochloride (Compound 497)

Melting point: 221-223℃.

NMR (DMSO-d_6, δ): 1.00-1.25 (m, 5H), 1.62 (m, 2H), 1.90 (m, 2H), 2.25 (s, 6H), 2.37 (m, 2H), 2.64 (m, 2H), 3.42 (s, 2H), 7.24 (s, 1H), 7.28 (d, J=8.4Hz, 2H), 7.53 (d,

J=8.4Hz, 2H), 8.05 (s, 1H), 11.31 (br, 1H).

Example 82: N-(3-(((4-pyperidinylmethyl)amino)methyl)phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide 2hydrochloride (Compound 312)

Melting point: 212-214℃.

NMR (DMSO-d_6, δ): 1.40 (m, 2H), 1.94 (m, 2H), 2.00 (m, 1H), 2.85 (m, 4H), 3.26 (m, 2H), 4.16 (s, 2H), 7.37-7.40 (m, 2H), 7.48 (t, J=7.8Hz, 1H), 7.70-7.76 (m, 2H), 8.16 (s, 1H), 8.79 (br, 1H), 8.95 (br, 1H), 9.29 (br, 2H), 10.81 (s, 1H), 12.32 (br, 1H).

Example 83: N-(4-((4-(1-pyperidinyl)-1-pyperidinyl)methyl)phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide 2hydrochloride (Compound 526)

Melting point: 264-267℃.

NMR (DMSO-d_6, δ): 1.39 (m, 1H), 1.65-2.31 (m, 10H), 2.88 (m, 4H), 3.31 (m, 4H), 4.26 (s, 2H), 7.38 (s, 1H), 7.59 (d, J=8.4Hz, 2H), 7.68 (d, J=8.4Hz, 2H), 8.13 (s, 1H), 10.82 (s, 1H), 12.31 (s, 1H).

Example 84: N-(2-(2-dimethylaminoethyl)-2,3-dihydro-1H-isoindol-5-yl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide 2hydrochloride (Compound 608)

Melting point: 196-199℃.

NMR (DMSO-d_6, δ): 2.86 (s, 6H), 3.56 (m, 2H), 3.82 (m, 2H), 4.65 (m, 4H), 7.37 (s, 1H), 7.42 (d, J=8.4 Hz, 1H), 7.51 (d, J=8.4Hz, 1H), 7.73 (s, 1H), 8.12 (s, 1H), 10.80 (s, 1H), 12.30 (s, 1H).

Example 85: N-(2-(3-dimethylaminopropyl)-2,3-dihydro-1H-isoindol-5-yl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide 2hydrochloride (Compound 611)

Melting point: 207-210℃.

NMR (DMSO-d_6, δ): 2.18 (m, 2H), 2.77 (s, 6H), 3.20 (m, 4H), 4.61 (m, 4H), 7.37 (s, 1H),

7.39 (d, J=8.1Hz, 1H), 7.51 (d, J=8.1Hz, 1H), 7.71 (s, 1H), 8.13 (s, 1H), 10.80 (s, 1H), 10.92 (s, 1H).

Example 86: N-(4-(2-dimethylaminomethyl-1-pyperidinylmethyl)phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide 2hydrochloride (Compound 482)

Melting point: 230-233℃.

NMR (DMSO-d_6, δ): 1.18-1.99 m, 6H), 2.85 (s, 6H), 3.09 (m, 1H), 3.36 (m, 1H), 3.80 (m, 1H), 4.14 (m, 1H), 4.27 (m, 1H), 4.42 (m, 1H), 4.81 (m, 1H), 7.37 (s, 1H), 7.66-7.69 (m, 4H), 8.13 (s, 1H), 10.81 (s, 1H), 12.31 (s, 1H).

Example 87: N-(4-(2-(2-dimethylaminoethyl)-1-pyperidinylmethyl)phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide 2hydrochloride (Compound 491)

Melting point: 215-225℃.

NMR (DMSO-d_6, δ): 1.75-2.07 (m, 6H), 2.79 (s, 6H), 2.93-3.40 (m, 6H), 4.20 (m, 1H), 4.34 (m, 1H), 4.71 (m, 1H), 7.38 (s, 1H), 7.67-7.77 (m, 4H), 8.13 (s, 1H), 10.82 (s, 1H), 12.32 (s, 1H).

Example 88: N-(4-(3-amino-1-pyrrolidinylmethyl)phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide 2hydrochloride (Compound 436)

Melting point: 217-220℃.

NMR (DMSO-d_6, δ): 2.11 (m, 2H), 3.34-3.98 (m, 5H), 4.41 (s, 2H), 7.36 (s, 1H), 7.62-7.68 (m, 4H), 8.12 (s, 1H), 10.80 (s, 1H), 12.3 (s, 1H).

Example 89: N-(4-((S)-2-dimethylaminomethyl-1-pyrrolidinylmethyl)phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide 2hydrochloride (Compound 263)

Melting point: 245-250℃.

NMR (DMSO-d_6, δ): 1.93-1.99 (m, 4H), 2.81 (s, 6H), 3.15-3.45 (m, 3H), 3.83-3.94 (m,

2H), 4.17 (m, 1H), 4.74 (m, 1H), 7.38 (s, 1H), 7.69 (m, 4H), 8.13 (s, 1H), 10.82 (s, 1H), 12.30 (s, 1H).

Example 90: N-(4-(4-pyperidinylaminomethyl)phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide 2hydrochloride (Compound 263)

Melting point: 245-250℃.

NMR (DMSO-d_6, δ): 1.89-1.99 (m, 4H), 2.24-2.29 (m, 2H), 2.92 (m, 2H), 3.15 (m, 1H), 4.14 (s, 2H), 7.38 (s, 1H), 7.65 (m, 4H), 8.13 (s, 1H), 10.79 (s, 1H), 12.32 (s, 1H).

Example 91: N-(4-((4-aminobutylamino)methyl)phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide 2hydrochloride (Compound 721)

Melting point: 205-210℃.

NMR (DMSO-d_6, δ): 1.60-1.72 (m, 4H), 2.77-2.88 (m, 4H), 4.09 (s, 2H), 7.38 (s, 1H), 7.58 (d, J=8.4Hz, 2H); 7.65 (d, J=8.4Hz, 2H), 8.13 (s, 1H), 10.79 (s, 1H), 12.32 (s, 1H).

Example 92: N-(4-((5-aminopentylamino)methyl)phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide 2hydrochloride (Compound 727)

Melting point: 215-219℃.

NMR (DMSO-d_6, δ): 1.35-1.66 (m, 6H), 2.75-2.82 (m, 4H), 4.11 (s, 2H), 7.27 (s, 1H), 7.58 (d, J=8.1Hz, 2H), 7.65 (d, J=8.1Hz, 2H), 8.14 (s, 1H), 10.79 (s, 1H), 12.32 (s, 1H).

Example 93: N-(4-((N-methyl-N-(4-methylaminocyclohexyl)) amino) methyl) phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide 2hydrochloride (Compound 743)

Melting point: 254-257℃ (decomposition).

NMR (DMSO-d_6, δ): 1.37 (m, 2H), 1.63 (m, 2H), 2.18-2.32 (m, 4H), 2.51 (s, 3H), 2.58 (d, J=4.8Hz, 3H), 2.87 (m, 1H), 3.01 (m, 1H), 4.17 (d, J=13.2Hz, 1H), 4.43 (d, J=13.2Hz,

1H), 7.40 (s, 1H), 7.62 (d, J=8.4Hz, 2H), 7.71 (d, J=8.4Hz, 2H), 8.15 (s, 1H), 8.82 (br, 2H), 10.18 (br, 1H), 10.84 (s, 1H), 12.28 (s, 1H).

Test Example: Inhibitory activity of the medicament of the present invention against P-GS1 phosphorylation by bovine cerebral TPK1:

A mixture containing 100 mM MES-sodium hydroxide (pH 6.5), 1 mM magnesium acetate, 0.5 mM EGTA, 5 mM β-mercaptoethanol, 0.02% Tween 20, 10% glycerol, 12 μg/ml P-GS1, 41.7 μM [γ-^{32}P] ATP (68 kBq/ml), bovine cerebral TPK1 and a compound shown in Table (a final mixture contained 1.7% DMSO deriving from a solution of a test compound prepared in the presence of 10% DMSO) was used as a reaction system. The phosphorylation was started by adding ATP, and the reaction was conducted at 25°C for 2 hours, and then stopped by adding 21% perchloric acid on ice cooling. The reaction mixture was centrifuged at 12,000 rpm for 5 minutes and adsorbed on P81 paper (Whatmann), and then the paper was washed four times with 75 mM phosphoric acid, three times with water and once with acetone. The paper was dried, and the residual radioactivity was measured using a liquid scintillation counter. The results are shown in the table below. The test compound markedly inhibited the P-GS1 phosphorylation by TPK1. The results strongly suggest that the medicaments of the present invention inhibit the TPK1 activity, thereby suppress the Aβ neurotoxicity and the PHF formation, and that the medicaments of the present invention are effective for preventive and/or therapeutic treatment of Alzheimer disease and the above-mentioned diseases.

Table 2

Example No.	Compound No.	IC_{50} (μM)
2	679	1.2
3	43	6.3
5	23	1.9
6	51	0.85
11	101	9.0
13	678	2.6
19	680	3.6
20	682	5.4
21	684	5.7
22	688	4.5
23	704	5.9
24	710	8.3
25	714	5.0
26	719	2.1
28	689	0.70
29	685	0.49
30	720	0.26
31	683	1.3
32	681	0.72
33	705	0.64
34	61	0.55
35	534	1.6
36	119	0.42
37	133	0.24
38	470	0.22
39	537	0.20
40	175	0.065
41	217	5.3
42	221	1.7
44	232	1.1
45	237	0.39
46	143	0.26
47	155	0.64
48	161	0.48
49	231	4.3
50	173	1.1
51	147	0.95
54	404	0.43
55	195	0.11
56	169	0.044
57	360	0.11
58	300	0.016
59	53	0.46
60	52	1.0
62	532	2.1
63	547	0.50
65	83	0.66
66	85	0.57
68	75	0.54
69	605	0.22
70	580	0.54
71	577	0.079
72	183	0.032
73	486	0.0080
75	388	0.029
76	538	0.0062
77	485	0.060
78	479	0.032
79	296	0.017
80	488	0.018
81	497	0.019
82	312	0.063
83	526	0.044
85	611	0.039
87	491	0.038
88	436	0.052
90	263	0.020
91	721	0.016
92	727	0.025
93	743	0.019

Formulation Example

(1) Tablets

The ingredients below were mixed by an ordinary method and compressed by using a conventional apparatus.

Compound of Example 6	30 mg
Crystalline cellulose	60 mg
Corn starch	100 mg
Lactose	200 mg
Magnesium stearate	4 mg

(2) Soft capsules

The ingredients below were mixed by an ordinary method and filled in soft capsules.

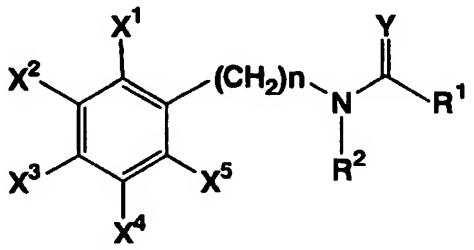
Compound of Example 13	10 mg
Olive oil	300 mg
Lecithin	20 mg

Industrial Applicability

The medicaments of the present invention have TPK1 inhibitory activity and are useful for preventive and/or therapeutic treatment of diseases caused by abnormal advance of TPK1 such as Alzheimer disease.

CLAIMS

1. A carboxyamido derivative represented by formula (I) or a salt thereof, or a solvate thereof or a hydrate thereof:



(I)

wherein R^1 represents 2-hydroxybenzimidazolyl group which may be substituted or 2-hydroxynaphthoimidazolyl group which may be substituted;

Y represents oxygen atom or sulfur atom;

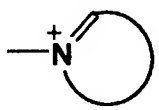
R^2 represents hydrogen atom or an alkyl group having from 1 to 5 carbon atoms;

n represents 0, 1 or 2;

X^1, X^2, X^3, X^4 and X^5 represent

(1) at least one of them represents a group represented by –P-A-Q-Z

in which symbol "P" and "Q" independently represent a bond or an alkylene group having from 1 to 5 carbon atoms, symbol "A" represents a bond, oxygen atom, sulfur atom, -SO- or $-SO_2-$, symbol "Z" represents (a) NR^3R^4, (b) $N^+R^5R^6R^7$, or a group represented by formula (c):

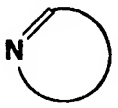


(c)

in which R^3 and R^4 independently represent hydrogen atom, an alkyl group having from 1 to 15 carbon atoms which may be substituted, an aryl group having from 6 to

12 carbon atoms which may be substituted, a heterocyclic group which may be substituted, R^8-CO-, R^8-O-CO- or R^8-SO_2- (R^8 represents an alkyl group having from 1 to 15 carbon atoms which may be substituted, an aryl group having from 6 to 12 carbon atoms which may be substituted, or a heterocyclic group which may be substituted), or R^3, N and R^4 may combine together to form a nitrogen-containing heterocyclic group which may be substituted; R^5, R^6 and R^7 independently represent an alkyl group having from 1 to 15 carbon atoms which may be substituted, an aryl group having from 6 to 12 carbon atoms which may be substituted, a heterocyclic group which may be substituted, or R^5, N and R^6 may combine together to form a nitrogen-containing heterocyclic group which may be substituted; and

the group of the formula:



represents a nitrogen-containing heterocyclic group having one or more sp^2 nitrogen atoms which may be substituted; or

(2) neighboring X^1 and X^2, X^2 and X^3, X^3 and X^4, or X^4 and X^5 may combine together with the benzene ring to form an isoindoline ring which may be substituted or a tetrahydroisoquinoline ring which may be substituted; and

(3) the rest of X^1, X^2, X^3, X^4 and X^5 independently represent hydrogen atom, an alkyl group having from 1 to 5 carbon atoms, or an alkoxyl group having from 1 to 5 carbon atoms.

2. The compound or a salt thereof, or a solvate thereof or a hydrate thereof according to claim 1, wherein R^2 represents hydrogen atom.

3. The compound or a salt thereof, or a solvate thereof or a hydrate thereof according to claim 2, wherein X^1 and X^5 represent hydrogen atom.

4. The compound or a salt thereof, or a solvate thereof or a hydrate thereof according to claim 3, wherein n represents 0 or 1.

5. The compound or a salt thereof, or a solvate thereof or a hydrate thereof according to claim 4, wherein Y represents oxygen atom.

6. The compound or a salt thereof, or a solvate thereof or a hydrate thereof according to claim 5, wherein R^1 represents 2-hydroxybenzimidazolyl group, 5,6-dichloro-2-hydroxybenzimidazolyl group or 2-hydroxynaphthoimidazolyl group.

7. A compound selected from the group consisting of:

N-(4-(4-piperidyl)methylaminomethylphenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazol-1-carboxyamide;

N-(4-(4-aminomethyl-1-pyperidinylmethyl)phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide;

N-(4-(4-(2-aminoethyl)-1-pyperadinylmethyl)phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide;

N-(4-(((3-pyperidinylmethyl)amino)methyl)phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide;

N-(4-(4-dimethylaminomethyl-1-pyperidinylmethyl)phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide;

N-(4-(4-(2-dimethylaminoethyl)-1-pyperidinylmethyl)phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide;

N-(4-((4-aminobutylamino)methyl)phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide; and

N-(4-((N-methyl-N-(4-methylaminocyclohexyl)) amino) methyl) phenyl)-5,6-dichloro-2-hydroxy-1H-benzimidazole-1-carboxamide

or a salt thereof, or a solvate thereof or a hydrate thereof.

8. A medicament which comprises as an active ingredient a substance selected from the group consisting of a carboxyamido derivative and a physiologically

acceptable salt thereof, and a solvate thereof and a hydrate thereof according to any one of claims 1 to 7.

9. The medicament according to claim 8, which is used for preventive and/or therapeutic treatment of a disease caused by tau protein kinase 1 hyperactivity.

10. The medicament according to claim 8, which is used for preventive and/or therapeutic treatment of a neurodegenerative disease.

11. The medicament according to claim 10, wherein the disease is selected from the group consisting of Alzheimer disease, ischemic cerebrovascular accidents, Down syndrome, cerebral bleeding due to cerebral amyloid angiopathy, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration and frontotemporal dementia.

12. A tau protein kinase 1 inhibitor comprising as an active ingredient a substance selected from the group consisting of a substance selected from the group consisting of a carboxyamido derivative and a salt thereof, and a solvate thereof and a hydrate thereof according to any one of claims 1 to 7.

INTERNATIONAL SEARCH REPORT

National Application No
PCT/JP 00/08690

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D235/26 C07D235/02 C07D401/12 A61K31/4184 A61P7/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	EP 0 523 013 A (BOEHRINGER INGELHEIM ITALIA) 13 January 1993 (1993-01-13) claim 1; example 1 --- -/--	1-12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 March 2001	26/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Härtinger, S

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	TOLNAY M ET AL: "REVIEW: TAU PROTEIN PATHOLOGY IN ALZHEIMERS'S DISEASE AND RELATED DISORDERS" NEUROPATHOLOGY AND APPLIED NEUROBIOLOGY,BLACKWELL SCIENTIFIC PUBLICATIONS, LONDON,GB, vol. 25, no. 3, June 1999 (1999-06), pages 171-187, XP000974565 ISSN: 0305-1846 abstract; figure 10 ---	1-12
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